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FASCIOLIASIS IN MAN: AN OUTBREAK IN HAMPSHIRE

BY

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AND

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During the autumn of 1958, in the Hampshire market town of Ringwood (population 7,000), several patients presented themselves with a mysterious illness characterized by pain in the right hypochondrium and an irregular pyrexia lasting over six weeks. The most striking finding in each case was the presence of a marked eosinophilia. Some form of helminthiasis was naturally suspected, and the symptoms suggested the possibility of infection with the liver fluke *Fasciola hepatica*. This theory was supported by the evidence of a veterinarian that the incidence of the infection among local farm animals was very high. A preliminary notification of this outbreak has been published (Facey, 1959).

Six cases are here reported, in five of which the diagnosis was subsequently confirmed by the finding of ova of *F. hepatica* in the faeces. Several other cases with similar symptoms were seen, but have not been included because the diagnostic evidence was not fully conclusive.

So far as we can discover this is the first occasion that epidemic infection with this helminth has been recorded in Britain. A search of the records back to 1903 has revealed reports of 12 cases, but all were isolated observations and in most of them the parasite was found at operation or necropsy (Ward, 1911; Owen, 1928; Patterson, 1928; Biggart, 1937; Manson-Bahr and Walton, 1941; Shaw and Clyne, 1941; O'Donnell, 1949; Murphy and Pascall, 1950, three isolated cases; Ramage, 1951; Catchpole and Snow, 1952). Ward refers to four earlier cases, bringing the number up to 16 in all. Several hundred cases have occurred abroad, including a number of outbreaks of acute illness due to the invasive stage of the disease. The countries most affected have been Latin America, France, Algeria, and Russia.

In the present communication the world literature is reviewed and our own cases are reported in some detail in the expectation that other outbreaks will come to light in this country from time to time.

The Outbreak

It is probable that three aetiological factors have combined to cause this outbreak. The disease is endemic in the Ringwood district of the Avon Valley, where nearly 100% of the cattle in some herds are infected and sheep cannot be reared; secondly, there are a number of natural watercress beds near by; and, thirdly, we have the precipitating cause, the wet summer of 1958.

All the patients live in this area and all of them were in the habit of eating watercress frequently.

The first patient, a general practitioner, was treating himself until one of us (R. V. F.), called in as pathologist, took charge of the case. After investigations at home and in hospital the patient was sent to London with a confident diagnosis of fascioliasis. At the Hospital for Tropical Diseases the diagnosis was confirmed by the finding of the ova of *F. hepatica* in the faeces. Throughout nearly all his illness he has been under our close observation.

The other patients were seen in neighbouring hospitals and at the laboratory of the Royal Victoria Hospital, Bournemouth. The two general practitioners principally concerned soon became able to spot likely cases by the liver tenderness, the fever, and asthenia, especially if accompanied by urticaria.

In five of the cases acute symptoms began during November, 1958, to January, 1959.

Case 1

A doctor aged 57 had always been healthy until 1958, when he had transient bouts of haematuria with pain after micturition, occurring in March and again in October. A blood count then showed eosinophils 2% (see Table) and a culture of the urine was sterile. There was a third attack on December 13, and after this he had an evening pyrexia, but he kept at work until December 20, when he had a rigor and his temperature rose to 104° F. (40° C.). A profuse sweat followed. The next morning he was afebrile, looked relaxed, and had no complaints, but from then on he kept to his room.

On examination the liver was enlarged two fingerbreadths below the costal margin; it was smooth and soft, and at this stage was not tender. No other abnormality was found except that a blood count gave eosinophils 19% (874/c.mm.).

The pyrexia and sweats continued during the next few weeks; temperature 98–103° F. (36.6–39.4° C.). He began to complain of slight discomfort over the whole abdomen. The only other symptoms were constipation, impaired powers of concentration, and increasing weakness.

An agglutination test against *Brucella abortus*, two blood cultures, and liver-function tests were all negative, but his condition was steadily deteriorating, and on January 2, 1959, he was admitted to Salisbury Infirmary. While in hospital

he complained for the first time of severe attacks of pain in the right hypochondrium, his liver increased in size and became tender on palpation, and he had an attack of urticaria. A skiagram of the chest was normal. Serological examination for leptospira and examination of faeces gave negative results. Treatment was empirical with antibiotics and antihistamines. There was no response and he discharged himself.

When seen again at home he was very weak and still had an irregular pyrexia. His pulse, previously unaffected, had increased to 120 a minute. Normally rotund and rubicund, he had lost 2 st. (12.7 kg.) in weight, his eyes and temples were sunken, and his skin had an extraordinary earthy colour. The bouts of pain were becoming more severe. The pain was "like toothache," always in the same spot, deep to the right lower ribs anteriorly. There was also referred pain at the tip of the right shoulder. The bouts came on suddenly, lasted a few hours, and then quickly passed off, leaving a feeling of discomfort, which persisted until the next bout. He was never jaundiced at any time.

When the case was reviewed at the end of January the most significant abnormality was thought to be the eosinophil count, particularly since two other patients (Cases 2 and 3) showing the same abnormality were then under investigation. The liver fluke was suspected, and inquiries confirmed the high incidence among farm animals in the district. All three patients declared that they were habitual consumers of watercress, and as they were all febrile with "liver pain" and two had enlarged tender livers it was thought that a presumptive diagnosis had been established.

In view of the weakened condition of our patient (Case 1) it was decided to send him to the Hospital for Tropical Diseases for treatment, though examination of the faeces had, so far, been negative.

On admission on February 5 the liver was enlarged four fingerbreadths below the costal margin, firm, regular, and tender. No other physical signs were noted. Examination of faeces revealed scanty operculated ova of *F. hepatica*. The complement-fixation test for fasciola was strongly positive; the total leucocyte count was 7,600/c.mm., of which 47% were eosinophils.

Treatment was started on February 10 with chloroquine 300 mg. eight-hourly. After a week he complained of dizziness and developed a marked tremor. The dose was cut to 150 mg. six-hourly and he tolerated this quite well. The pains soon stopped, and on February 22 he returned home.

While in London he had lost more weight, making a total of 3 st. (19 kg.), but the acute symptoms had subsided and on return home his liver was only two fingerbreadths below the costal margin. His colour was still earthy and had a greenish sheen. He completed the treatment by March 23—total chloroquine 33 g.—and started work in April. In March and again in July electrophoresis of his serum showed a considerable increase in gamma-globulin.

By December, 1959, he was almost free from symptoms and had regained some weight, but his liver was still slightly enlarged. His blood count was normal, eosinophils 5%, erythrocyte sedimentation rate 10 mm. in one hour, and the electrophoretic pattern of the serum had returned to normal. Live ova of *F. hepatica* were still present in the faeces.

(It is possible that the initial attacks of haematuria were due to ectopic flukes, but the normal count in October, 1958, suggests that at that time the larvae had not entered the liver.)

Case 2

A factory worker aged 48 who had always been healthy began to feel tired in November, 1958. On December 17 he started to have an irregular pyrexia, temperature 98.4–101° F. (36.9–38.3° C.), with some abdominal discomfort. Early in January, 1959, he got an aching pain in the right hypochondrium and right shoulder. He was a muscular man and neither liver nor spleen was palpable. He had lost 1 st. (6.4 kg.) in weight.

Investigations showed leucocytes 7,400/c.mm., eosinophils 47%. Agglutination tests against *Br. abortus* were negative. Two examinations of faeces were negative, but on February 17 scanty operculated ova of *F. hepatica* were found in them.

Treatment was then started with hydroxychloroquine sulphate 600 mg. daily, and in spite of some side-effects the treatment was continued for six weeks. At the end of this period he was ambulant, afebrile, and free from pain, but viable ova were still present in the stools. Early in May the pain and fever returned, the eosinophil count was 28%, and ova were still present in the faeces.

He was given two courses, each of 18 injections, of emetine hydrochloride ½ gr. (32 mg.) subcutaneously. After these he remained afebrile and free from symptoms. He put on weight and returned to work. From the middle of the first course of emetine onwards the faeces were free from ova. Six tests have been made, the last in January, 1960, when the eosinophil count was also normal (4%). It is hoped he is cured.

Case 3

A housewife aged 45 had a history of malaria in the Sudan in 1944. She returned to England in 1945, and in 1957 she had a cholecystectomy for gall-stones. Early in November, 1958, she complained of abdominal discomfort in the right upper quadrant and pains "all over her." A pain in the right shoulder was aggravated by coughing. In December she began to have sudden attacks of dull pain in the epigastrium and right hypochondrium, "nearly passing out" with them. The liver was just palpable, but the spleen could not be felt. There was a slight irregular pyrexia.

The eosinophil count was 18%, later rising to 40%. The Westergren sedimentation rate was 40 mm. A liver biopsy was carried out in Southampton Hospital, and Dr. R. A. Goodbody reported: "The portal tracts are infiltrated by polymorphs, histiocytes, and quite large numbers of eosinophil leucocytes" (Fig. 1).

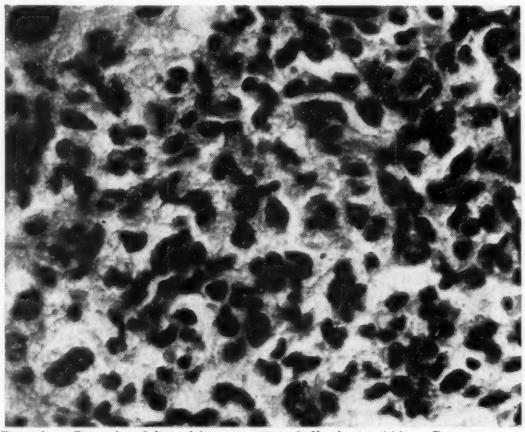

FIG. 1.—Case 3. Liver biopsy. Fascioliasis (×450). By courtesy of Dr. R. A. Goodbody. (Photomicrograph by Mr. J. Wilson.)

After two negative examinations a specimen of faeces examined on February 18 showed scanty ova of *F. hepatica*.

Treatment was started with chloroquine sulphate 800 mg. daily, but was not well tolerated. The dose was reduced and by the end of three months 30 g. had been given. She has since had repeated bouts of abdominal discomfort, but so far has refused further treatment. Ova of *F. hepatica* were still present in the faeces in January, 1960, though her eosinophil count was only 2%.

Case 4

A housewife aged 56 was in Kenya from 1930 to 1951. While there she had amoebic dysentery and malaria. She had suffered from migraine for some years, and in August, 1958, began to lose weight. In September she complained of weakness, cough, tightness across the upper part of her

chest, and slight pain at the left base on inspiration. There were signs of bronchitis but no fever, and a chest *x*-ray film was negative. Antibiotics brought no improvement. From January to March, 1959, she had an irregular pyrexia with a temperature of 98 to 101° F. (36.7–38.3° C.). By March 7 she had lost 2 st. (12.7 kg.) in weight, had been bedridden for eight weeks, and was deteriorating. She was admitted to hospital in Bournemouth. On examination the tip of the spleen was just palpable but there were no other physical signs. The liver was not enlarged. A routine blood count showed eosinophils 44%, and an examination of faeces next morning showed ova of *F. hepatica*.

On March 13 treatment was started with chloroquine sulphate 900 mg. daily, but she soon developed tremors, marked visual incoordination, nightmares, and dryness of the skin. The dose was reduced to 600 mg. and eventually to 150 mg. daily. A total of 35 g. was given.

It was soon impossible to feel the spleen, and after the treatment she regained some of her lost weight. Her general health improved. In October, 1959, a blood examination showed leucocytes 7,500/c.mm., eosinophils 10%, E.S.R. 16 mm. in one hour. The faeces still contained a few ova of *F. hepatica*.

Case 5

A housewife aged 59 had a history of a perforated gastric ulcer in 1938 but no other significant illnesses. She moved to Ringwood and started to eat watercress on November 1, 1958 (she was able to fix this date precisely). The symptoms started suddenly on December 8 with severe epigastric pain which did not radiate. There was a transient urticarial rash. The pain eased and she was fairly well until May 30, 1959, when she had a sudden attack of pain in the right iliac fossa, moderate pyrexia, and another attack of urticaria. She vomited, and on June 4 the pain became worse. She was admitted to Salisbury Infirmary as a case of "acute abdomen." On examination the temperature was 99° F. (37.2° C.), the pulse was 96, and the tongue was clean. There was a hard and acutely tender mass in the right side of the abdomen. Though on palpation this mass was apparently continuous with the liver it did not move on respiration. It was dull on percussion. The chest was clear.

Investigations.—I.V.P. and barium enema showed no abnormalities. June 4: leucocytes 7,000/c.mm., eosinophils 32%, E.S.R. 46 mm. in one hour; plasma proteins normal; examination of faeces revealed the ova of *F. hepatica*; the urine was normal.

Treatment was started on June 19 with chloroquine sulphate 250 mg. t.d.s., and after two weeks the dose was increased to 200 mg. q.i.d. After 12 weeks she had taken 66 g. and was suffering from visual incoordination, giddiness, and anorexia. By this time, the middle of September, she had lost nearly 2 st. (12.7 kg.) in weight, but the mass had disappeared and the liver was not palpable. When seen again in March, 1960, she was well except for occasional niggling pains in the right hypochondrium. She was gaining weight. A blood examination showed 8% eosinophils. Liver-function tests were normal. The faeces contained a few ova of *F. hepatica*.

Case 6

A housewife aged 30 had a history of a short attack of pain in the right hypochondrium in 1957 but no other illness: In January, 1959, she had a violent attack of epigastric pain and a brief urticarial episode. In March she had a pain "like a stitch" under the right costal margin and referred pain in the right shoulder. There was an irregular pyrexia, the temperature reaching 103° F. (39.4° C.). The liver was just palpable and tender. By the end of April she had no symptoms except weakness and dyspepsia and there were no physical signs. The haemoglobin was 75%, leucocytes 14,000/c.mm., eosinophils 28%, E.S.R. 43 mm. in one hour. Examination of the faeces failed to show any ova, but the complement-fixation test for fasciola was strongly positive.

She was given a course of chloroquine sulphate, total 20 g. The eosinophils fell to 11%, and when seen in August she was free from symptoms and the faeces still contained no ova.

Comment

All the more important characteristics of the invasive phase were illustrated in the illness of the first patient, and with less severity in those of four of the others. With one exception they were all examples of the hepatic syndrome, with hepatomegaly in four cases. One patient (Case 4) showed the respiratory syndrome, probably due to ectopic flukes, and she alone had splenomegaly. Another (Case 5) probably had an ectopic fluke in the right iliac fossa which may have been due to a second infection.

It seems probable that the actual infection of at least two of the patients (Cases 1 and 5) took place in October or November, 1958. The ova were found in the faeces of the first three patients in February, 1959. If they were all infected at about the same time this allows a period of three to four months for the parasites to attain sexual maturity, the minimum possible.

Five patients were treated with chloroquine sulphate and one with hydroxychloroquine sulphate. Three of them took 30 g. or more in six weeks; in the others the dose had to be reduced. All complained of troublesome side-effects, especially tremors and visual disturbances. (Possibly the liver damage impaired their tolerance.)

Details of Cases

	Case 1				Case 2			Case 3		Case 4		Case 5		Case 6	
Date of onset of acute symptoms:	20/12/58				17/12/58			3/11/58		1/8/58		8/12/58		30/1/59	
	1958		1959		1959			1959		1959		1959		1959	
	Oct.	Dec.	Jan.	Mar.	Jan.	Feb.	May	Feb.	Apr.	Mar.	May	June	Sept.	Apr.	July
Haemoglobin (%)	104	100	80	78	94	108	88	87	—	75	83	95	86	75	88
,, (g. 100 ml.)	15·2	14·6	11·7	11·4	13·7	15·8	12·8	12·7	—	11·0	12·1	13·9	12·5	11·0	12·9
Leucocytes c.mm.	5,900	4,600	—	5,200	7,400	9,000	6,100	9,100	—	9,500	6,500	7,000	3,710	14,000	6,700
Eosinophils (%)	2	19	29	45	47	32	28	24*	—	44	9	32	9	8	11
,, c.mm.	118	874	—	2,340	3,478	2,880	1,708	2,184	—	4,180	585	2,240	333	4,000	737
E.S.R. (Wintrobe) mm. hour	3	29	47	49	15	21	43	15	—	38	14	46	16	43	10
Thymol units	—	—	6	5	—	—	1	4	—	—	—	—	—	—	1
Alkaline phosphatase units	—	—	18	19	—	—	31	9	—	—	—	—	—	—	6
Bilirubin (mg./100 ml.)	—	1·0	0·8	0·5	—	—	1·2	0·5	—	—	—	—	—	—	0·8
C.F.T.	—	—	—	+++	—	+++		+++		+++		+			+++
F. hepatica ova in faeces	—	—	Neg.	+ (Feb. 6)	Neg.	+	+	+	+	+	+	+	+	Neg.	Neg.

* When this patient was in the Southampton Hospital in January the eosinophil count was 40%.

Chloroquine quickly relieved the symptoms in every case but it completely failed to kill the flukes, for all the patients continued to pass ova with the exception of the last, in whose faeces they have never been found. All refused further treatment except one (Case 2) who had a relapse and was given two courses of emetine, after which the ova disappeared from his faeces.

Though all the patients were free from acute symptoms several still complained of occasional abdominal discomfort and at least four were still infected.

Blood Changes.—Every patient had a high eosinophilia, the average initial count being 34%. In only one case was there a leucocytosis. Anaemia was not a prominent feature, but a chance observation in one patient (Case 1) whose haemoglobin fell nearly 3 g. in a month may be of some significance. In December, 1958, films prepared from defibrinated and incubated blood showed marked spherocytosis and avid erythrophagocytosis, an abnormality not seen in straight films of his whole blood. The reticulocyte count was 1.8%, the Coombs test was positive, optimum A.H.G. dilution 1/16, but cold agglutinins were not detected at 4° C. or 20° C. The bilirubin was 1 mg./100 ml. These results are thought to suggest sensitization of the red cells to a circulating antibody. A high red-cell sedimentation rate was found in all cases, and it was sustained for some time after the acute symptoms subsided.

Liver-function tests were generally not very helpful, but electrophoretic studies showed an increase in serum gamma-globulin in four cases. The shape of the curve suggested that this was due to antibody formation. The complement-fixation test for fasciola was positive in all six cases. A *liver biopsy* (Case 3) showed a marked infiltration of eosinophils.

Faeces were examined for ova by a modified formol–ether method (Ridley and Hawgood, 1956), which proved very reliable. Ordinary flotation methods were not satisfactory. Care was taken in each case to ensure that the patient had eaten no offal for at least eight days before the test.

Review of the Literature

Valuable studies have been made by Burgi (1936), in Germany, who collected 186 cases from the literature; by Kourí (1948), in Cuba, with experience of 100 cases; by Rodriguez (1952), in Argentine, with 20 cases; by Rial *et al.* (1951), in Uruguay; and by Lavier and Marchal (1942), in France. It seems worth while to give a general description of the disease based on these publications and others, since the literature on the subject in English is somewhat scanty.

Aetiology and Natural History.—F. hepatica is normally a parasite of herbivora, particularly sheep. The mature flukes live in the bile-ducts of the host, their eggs being passed in the faeces. In wet and muddy conditions the eggs hatch, giving rise to motile forms, the miracidia which enter snails (Figs. 2 and 3), where they multiply and whence they emerge as tadpole-like cercariae, soon losing their tails to encyst on water-side vegetation as just-visible snow-white cysts (Brumpt, 1949). Three wet summer months are necessary to permit the development of the snail, *Limnaea truncatula*, and the fluke. Outbreaks may occur in animals or humans in the following autumn or spring (Ollerenshaw, 1958). In all countries where human fascioliasis has been reported watercress has been found to be the usual vehicle. When the infected herb is ingested the parasite excysts in the duodenum of the host, penetrates the gut wall, passes

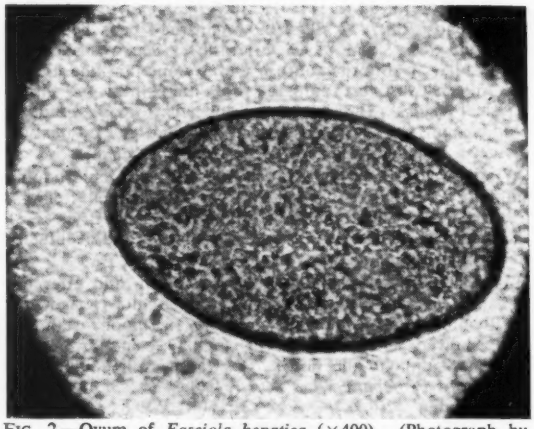

FIG. 2.—Ovum of *Fasciola hepatica* (×400). (Photograph by Mr. R. H. Hunt.)

through the peritoneal cavity, and enters the dome of the liver through Glisson's capsule. The larvae plough through the liver substance to enter the bile-ducts, where they grow to maturity and start to lay eggs. From the time of ingestion of the infected vegetation this process takes three or four months (Krull and Jackson, 1943). The site of the parasite and its stage of development determine the "phase" of the disease, a distinction of prognostic and therapeutic importance.

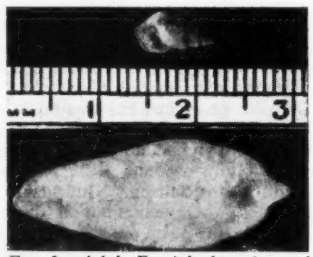

FIG. 3.—Adult *Fasciola hepatica* and its intermediate host, the snail *Limnaea truncatula*. (Photograph by Mr. R. H. Hunt.)

Phases of the Disease

The acute illness of the *invasive phase* is due to allergic, immune, and toxic local and general reaction to the presence of *larvae in the tissues* (Craig and Faust, 1951). Liver biopsies* have shown the paths of the larvae, leaving tracks of necrosis with infiltration of histiocytes, of polymorphs, and notably of eosinophils. There are vascular thromboses and associated areas of necrosis (Claisse and Hartmann, 1954).

The *symptoms* of this phase have been well described in a report on 52 Cuban cases by Arenas *et al.* (1948). Similar observations have been recorded in European and Algerian cases by Martin *et al.* (1944),, Sédallian *et al.* (1949), Brouet *et al.* (1951), Meriel *et al.* (1954), Bickel and Secretan (1954), Lemoine (1954), Jacquemin and Rool (1957), and Michon *et al.* (1957). Levina (1950), recording 20 cases in the Moscow district, gave almost identical descriptions.

After a short period of dyspepsia and, perhaps, of slight fever, the onset is usually abrupt, with high fever and abdominal pain.

*A good description of the lesions due to the similar fluke, *F. gigantica*, is given by Stemmermann (1953), who ascribes the toxic effects to digestive enzymes liberated by the larvae.

The *pain*, which can be excruciating, is likened to toothache or cramp, coming on in waves, dragging, less often stabbing or a "stitch"; it is often aggravated by coughing or movement. It lasts some hours, and on passing leaves a feeling of weight which persists until the next attack. The pain may be general over the whole abdomen, but it soon becomes localized in the right hypochondrium or sometimes in the epigastrium. Radiation to the tip of the right shoulder is common.

The *liver* is often much enlarged, sometimes reaching down to the right iliac fossa. Arenas *et al.* found some enlargement in 73% of their cases. The hepatomegaly may follow some time after the pain, or it may precede it.

The *fever* completes the triad which, with the eosinophilia, is almost diagnostic of the condition. The sudden rise of temperature at the onset may reach 104° F. (40° C.). Sometimes it is persistent at a somewhat lower level for a week or two, but characteristically it oscillates, with a rise to 102–103° F. (38.9–39.5° C.) at the end of the day. It may last for eight weeks or more. According to Arenas *et al.* fever is invariably present. An occasional rigor is not uncommon, and sweats, often severe enough to suggest brucellosis, are the rule.

Asthenia, which may be extreme, occurs in most cases. The limbs feel heavy.

Wasting can be very great in severe cases. Anorexia, capricious appetite, flatulence, vomiting, diarrhoea, and constipation are frequently reported.

Urticaria is often an early episode, though it sometimes occurs at the height of the attack. It is a useful diagnostic pointer. An earthy coloured skin is a striking abnormality which, when present, is of diagnostic importance. It may lead to a false diagnosis of Addison's disease.

Splenomegaly occurs in 25% of cases.

Respiratory symptoms, especially cough, are common. There may be crepitations at the right base with a pleural rub and sometimes haemoptysis. Polyadenopathies have been reported, especially in children (Rial *et al.*, 1951). Other patients may have headache, insomnia, nightmares, muscle and joint pains, transitory hemiplegia, dermatographia, abdominal rigidity, meteorism, melaena, or epistaxis. In spite of this imposing list there is seldom much malaise.

Recovery may occur by the parasites being evacuated through the intestine or they may become shut off and calcified (visible radiographically). If live adult flukes are retained in the bile passages the disease passes into the next stage.

The Latent Period.—The symptoms now subside suddenly and for months or years the patient may suffer nothing worse than indigestion, though there are sometimes one or more relapses with return of the acute symptoms.

The *obstructive phase* of the disease has been described in English reports already quoted and by d'Allaines *et al.* (1942), Nañagas *et al.* (1954), Derom *et al.* (1956), and many others. Since the treatment of this disease depends upon the use of protoplasmic poisons the question of prognosis becomes very important; but unfortunately the percentage of cases which pass into the obstructive phase has not been ascertained, as so few observers have followed up their cases long enough.

A good account of the *pathology* has been given by Biggert (1937). Adult flukes in the bile-ducts irritate the biliary epithelium, causing adenomatous thickening and dilatation of the ducts. Malignant changes have occurred in animals and in clonorchis infections of man (Hoeppli, 1933), but no human cases have been ascribed to fascioliasis according to Bürgi (1936).

If many flukes are present, atrophy and fibrosis may lead to biliary cirrhosis (Manson-Bahr and Walton, 1941). Sometimes the flukes eat their way back into the liver and seed it with their eggs (Craig and Faust, 1951). But the commonest sequel is obstruction of the bile-ducts by the flukes or by calculi which often accompany them. Secondary bacterial infection may cause acute inflammatory lesions of the biliary tree.

Detailed description of the obstructive phase is beyond the scope of this article except for the differential diagnosis from the invasive phase. Here the eosinophil count is the significant factor. It is seldom much raised in the obstructive phase. A high count is a contra-indication to operation according to Faiguenbaum *et al.* (1958).

Ectopic Fascioliasis.—One of the strangest manifestations of fasciola infections of man is the occasional appearance of immature flukes in sites other than the liver, most commonly in the abdominal wall. The parasites never grow to maturity in such positions and they may later continue their migration to the liver; they may become calcified or, more characteristically, become incorporated in a granuloma which has sometimes been observed itself to migrate subcutaneously towards the liver (Catchpole and Snow, 1952). Sometimes the young flukes enter the blood-stream and pass to distant parts of the body (Ortiz, 1934–5; Shaw and Clyne, 1951; Neghme and Ossandon, 1943).

Halzoun.—In the Levant there occurs a form of pharyngeal fascioliasis known by this name. This is a direct infection derived from the ingestion of raw liver of animals in sacrificial rites.

Differential Diagnosis

In the *differential diagnosis* acute fevers such as brucellosis and typhoid must be excluded. Other parasitic diseases, ascariasis, trichinosis, schistosomiasis, filariasis, and in young children, visceral larva migrans (Beaver *et al.*, 1952) have to be considered. Some cases may simulate Loeffler's syndrome, tropical eosinophilia, the reticuloses, or eosinophilic leukaemia.

Treatment

We have found no reports of fully controlled clinical trials. Kourí and Arenas (1932) introduced the emetine treatment, advising a course of 5 mg./kg. of body weight given in a daily dose of 40 mg. of emetine hydrochloride subcutaneously or intramuscularly. This procedure has been widely adopted (Martin *et al.*, 1944; Minning, 1952). Antimony compounds, extract of male fern, and other toxic anthelmintics have often been given, but the weight of evidence favours emetine as the drug of choice.

Prophylaxis

Ideally watercress should be grown under artificial conditions and the inoculum should be healthy (Friess, 1946). In practice it is often cut from natural beds fed by streams running through pastures (Brumpt and Lavier, 1939).

Discussion

A few hundred cases of human fascioliasis have been reported from various parts of the world. Rare in England, cases in the U.S.A. seem to be rarer still. Adams (1934), reporting a case, could find no other records there. This is surprising, as Olsen (1948) found that a third of the jack-rabbits of Texas were infected, forming a "vast reservoir of infection." The incidence among farm animals in England, already high, increased very much during the wet summer of 1958. The number of human cases in France has risen greatly in the last few years, so it is reasonable to expect outbreaks here.

According to Belding (1952) only 5% of cases are diagnosed in the invasive phase. This must be due to unfamiliarity with the disease. The acute symptoms call for a blood count, which will often reveal an eosinophilia higher than is found in most other diseases in temperate climates. The history of having eaten watercress is significant, especially in endemic areas. Confirmation may be sought in the complement-fixation test (Fairley and Williams, 1923; Mohr *et al.*, 1951) or the intradermal test (Lavier and Stefanopoulo, 1944), though there has been little experience of these reactions in this country so far.

Ova will not be found during the first three to four months after infection, since the parasites have not attained sexual maturity. They are said to be first detected in bile from a duodenal tube (Coudert, 1952). A method devised by Kourí has been described (Gradwohl, 1943). A week or two later they are to be seen in the faeces, soon becoming quite numerous, though their demonstration by ordinary flotation techniques is unreliable. A modified formol–ether method has given good results. In the later stages of the disease the ova become very scanty and often cannot be found at all, while the eosinophil count may be normal. Careful history-taking is then the only hope for a "medical" diagnosis of the underlying parasitic aetiology.

Many observers have stressed the importance of starting emetine treatment while the parasite is still in the larval form and said to be most susceptible. This course has not found favour with orthodox opinion in this country as it means using an unproved remedy for an unproved disease. We ourselves have found it a hard decision to take, but future experience may well show that early treatment with emetine offers the best hope of cure.

In view of the successful use of chloroquine in clonorchis infections (Chu, 1957) it had to be tried in fascioliasis. The effect on the symptoms in our cases was dramatic, but unfortunately it did not cure.

Anaemia occurs comparatively rarely in the invasive stage. It is usually described as "toxic" in origin, but our accidental findings in one case suggest that it is due to a red-cell-sensitizing antibody. It is interesting to note that Mello (1910) produced spherocytosis with an extract of dried flukes and that Flury and Leeb (1926) found that the excretions of flukes had haemolytic properties. The occurrence of a red-cell-sensitizing antibody in patients with other parasitic infections is reported by Zoutendyk and Gear (1950, 1959).

In an attempt to trace the course of the Ringwood outbreak watercress from a local bed in a cow pasture was fed daily to four newly weaned rabbits from June to October, 1959. The absence of any evidence of infection when the animals were killed in January, 1960, may well have been due to the exceptionally dry summer of 1959. The fact remains that many watercress beds in this country are wide open to infection. There is a need for some measure of control in endemic areas, especially after wet summers.

Summary

Though 16 isolated cases of fascioliasis have previously been recorded in this country this is the first *outbreak* to be reported.

At least six patients were affected, in five of whom the diagnosis was confirmed by finding the ova in the faeces.

All the patients were in the habit of eating watercress grown in natural beds.

Prolonged fever, pain in the right hypochondrium sometimes associated with hepatomegaly, asthenia, and often urticaria were the main symptoms, with, most significantly, a very high eosinophilia in every case.

The ova do not appear until three to four months after infection. They are best demonstrated by the formol–ether method. Ordinary flotation procedures are not satisfactory.

The anaemia found in one case appeared to be due to a red-cell sensitizing antibody.

Chloroquine was used probably for the first time in fascioliasis. This treatment relieved the symptoms dramatically but failed to cure.

Control of watercress beds in endemic areas is advised.

In the review of the world literature a general account of the disease is given.

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THE PITUITARY AND ADRENAL CORTEX IN GENERAL MEDICINE*

BY

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The Anterior Pituitary Gland

The hormones of the anterior pituitary gland include corticotrophin, thyrotrophin, gonadotrophin, prolactin, and growth hormone. They are polypeptides, and in some cases the amino-acid composition and sequence have been ascertained. Growth hormone shows a considerable degree of species specificity (Knobil and Greep, 1956) associated with differences in amino-acid sequence (Li and Papkoff, 1956). The anterior pituitary hormones are not easy to purify, and their estimation in body fluids and tissues is still in a very primitive stage.

Corticotrophin regulates the production of hydrocortisone and sex hormones by the adrenal cortex, and in its absence the adrenal stops secreting hydrocortisone although aldosterone production continues. Animal experiments have suggested that there may be two pituitary hormones acting on adrenal cortex—one affecting adrenal weight and the other concerned with metabolic activity (Liddle *et al.*, 1954). In addition to its effect on the adrenal cortex, corticotrophin has a direct effect on metabolism of fatty tissue with liberation of unesterified fatty acids (White and Engel, 1958); this effect is not seen with injections of corticotrophin and measurement of plasma unesterified fatty acids (Raben and Hollenberg, 1959). Corticotrophin also has a skin-pigmenting effect, independent of but similar to melanocyte-stimulating hormone (*British Medical Journal*, 1957). Bioassay methods for corticotrophin measurement are available, and increased plasma levels have been detected in Addison's disease and occasional cases of Cushing's syndrome secondary to a corticotrophin-producing pituitary adenoma or carcinoma (Clayton, 1958; Lipscomb and Nelson, 1959).

In the case of thyrotrophin, clinical evidence suggests that there is an exophthalmos-producing substance independent of the thyroid-stimulating hormone. This has been demonstrated experimentally in animals (Dobyns and Steelman, 1953). Although thyrotrophin plays an important part in the regulation of thyroid activity the gland can accumulate iodine and secrete thyroxine in the absence of the pituitary and presumably of any thyrotrophin. This has only been demonstrated in patients with thyrotoxicosis or thyroid adenomata (Becker, 1959; Gurling *et al.*, 1959).

Studies with growth hormone have been limited on account of its species specificity and because there is no simple method for its estimation in body fluids. It has been shown that as much growth hormone can be extracted from the pituitaries of adult humans as from those of growing children (Gershberg, 1957), but its role in adult metabolism and physiology has not yet been defined. Metabolic studies have been performed, using human and monkey growth hormone, and have shown nitrogen and calcium retention more marked in patients with deficiency of growth hormone than in normal subjects (Beck *et al.*, 1957). Increased urinary calcium excretion has been noted in several studies (Ikkos *et al.*, 1959; M.R.C. Clinical Endocrinology Committee, 1959). Growth hormone has an *in vivo* effect on fat-metabolism with elevation of the plasma unesterified fatty acids (Raben and Hollenberg, 1958). The possible role of growth hormone in complicated juvenile diabetes and in certain types of cancer is discussed later.

A fat-mobilizing substance has been found in plasma and in urine. Chalmers *et al.* (1958) have isolated it from urine, and found that it is increased on fasting and disappears after hypophysectomy. Whether it is identical with one of the known pituitary hormones has not yet been determined. It is a polypeptide, but does not have the same properties as corticotrophin or growth hormone (Chalmers, 1960, personal communication). Originally isolated in studies on obesity, its relationship to this and other human diseases is at present only a matter of speculation.

Total hypophysectomy by the transfrontal, transseptal-sphenoid (Heck *et al.*, 1957), and trans-antro-sphenoidal (Hamberger *et al.*, 1959) routes has been undertaken for a number of conditions, including juvenile diabetes with complications, disseminated cancer, especially of the breast or prostate, and malignant exophthalmos. The operation is a considerable undertaking in any of these conditions, and other methods of reducing pituitary function have been investigated. External irradiation by conventional and supervoltage techniques has been disappointing and may be hazardous, though

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external irradiation by high-energy proton-beams may be effective (Tobias *et al.*, 1958). Internal irradiation with γ-ray sources—radioactive gold and radon—is dangerous because the surrounding brain tissue and nerves may be affected. β-ray emitters are safer because of the reduced penetration of the rays. The most satisfactory isotope at present is yttrium-90, and the technique developed in Glasgow of screwing the pellets into the floor of the sella turcica is the best method of pituitary destruction so far developed (Forrest *et al.*, 1959).

An alternative method of reducing pituitary function was suggested by a report of Professor Dorothy Russell on the effect of stalk section (Russell, 1956). The Neurosurgical Unit at the Middlesex Hospital (the late Miss Diana Beck, Mr. Valentine Logue, Mr. F. L. Davies) carried out a small series of pituitary-stalk sections two to three years ago. The endocrine changes resulting from this operation have been followed, and have confirmed some of the reported results of animal experiments on the control of pituitary function. (Preliminary accounts of these cases have been given by Davies and Buxton, 1957; Buxton *et al.*, 1958.)

Pituitary-Stalk Section

This operation was performed on 15 patients between September, 1956, and March, 1957. Thirteen had carcinoma of the breast and one each of carcinoma of the prostate and adrenal. Three patients died within ten days of the operation. In 11 of the remaining 12, pituitary function was reduced and in six there was a remission of the malignant disease. Initially the operation was performed without steroid cover; the patients were drowsy after operation but responded to intravenous hydrocortisone. The urinary steroid excretions fell to a very low level (Fig. 6). There was an early striking

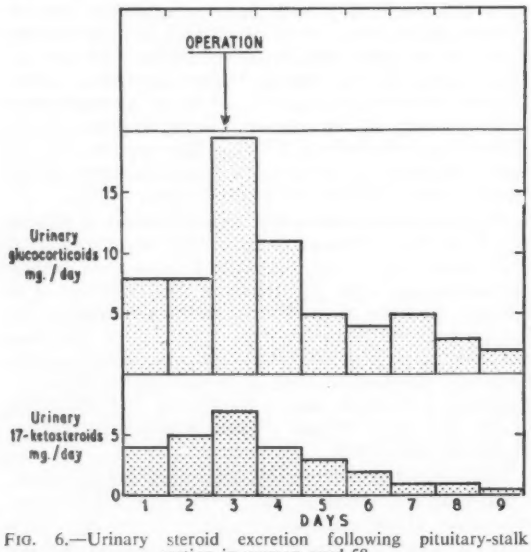


FIG. 6.—Urinary steroid excretion following pituitary-stalk section in woman aged 58.

fall of radioactive iodine uptake, but in all cases some thyroid function began to return at about 10 weeks. This could have been due to autonomous activity on the part of the thyroid gland or production of thyrotrophin by a pituitary not connected with the hypothalamus. The fact that the iodine uptake by the thyroid gland was suppressed by triiodothyronine (Fig. 7) suggests continued thyrotrophin production. Endocrine-function studies on patients surviving more than three months are shown in Table V. From gradual steroid withdrawal tests it appeared that adrenal function was at a very low level in three cases. The test in Case 12 was an acute steroid withdrawal; Dr. D. N. Baron reported the presence of 6.7 γ-free hydrocortisone per 100 ml. of plasma after three days off replacement therapy. The patient at this time had undoubted clinical evidence of acute adrenal insufficiency.

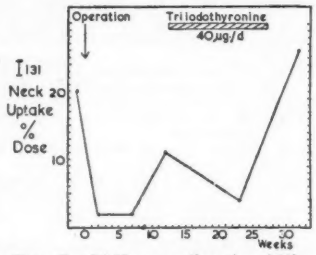


FIG. 7.—24-Hour radioactive iodine uptake by the thyroid gland after pituitary-stalk section in woman aged 51 (Case 18). Uptake suppressed by triiodothyronine.

The urinary excretion of follicle-stimulating hormone was followed in cases in which it was raised before stalk section. Drs. R. D. Bulbrook and F. C. Greenwood

TABLE V.—*Endocrine-function Tests in Patients Surviving Three Months after Pituitary-stalk Section*

Case	Time (Months Post-op.)	Adrenal Function	Thyroid ^{131}I Uptake (24 Hrs.)	Urinary Oestrogens (μg. 24 Hrs.)	Urinary F.S.H.
15	3	0	—	0	0
13	4	0	20%	—	—
10	6	—	14%	2·4	0
20	8	—	28%	—	—
16	12	0	30%	1·3	0
18	20	—	26%	6·3*	0
12	22	+	8%	0	0

* Zero for 12 months after operation.

estimated the urinary oestrogens. In Case 18 they disappeared from the urine after operation but reappeared 12 months later, and there was evidence of renewed activity of the neoplasm. It is not possible to say whether there had been regeneration of the hypothalamic-pituitary vascular channels, because hypophysectomy was undertaken. The pituitary fossa appeared empty and curettings showed on microscopy dense hyaline fibrous tissue with occasional cells of pituitary type.

Pathological specimens of the pituitary were obtained in most of these cases. Those from patients dying 12 months or more after the operation showed very little pituitary tissue.

Reports on the results of pituitary-stalk section have now been published from a number of centres. In patients with disseminated breast cancer it has generally been found that remissions are shorter than after total hypophysectomy (Baron *et al.*, 1958; Dugger *et al.*, 1958). In juvenile diabetics with retinitis the results have been disappointing, although reduction of insulin requirement has been noted (Javid *et al.*, 1958; Lundbaek *et al.*, 1960). Animal experiments have suggested that pituitary secretion of corticotrophin and gonadotrophin stops after stalk section (Fortier *et al.*, 1957), although thyrotrophin secretion may continue (Brown-Grant *et al.*, 1957). Van Wyk *et al.* (1960) have claimed that corticotrophin may still be secreted in response to stress but not to a reduction of the circulating level of hydrocortisone. Jessiman (1959) has suggested on clinical

grounds that growth-hormone secretion is reduced by stalk section, whereas that of prolactin continues (Ehni and Eckles, 1959).

Pituitary Surgery for Severe Exophthalmos

Treatment of severe exophthalmos is unsatisfactory. Various measures have been advocated, including triiodothyronine suppression, steroid therapy, orbital irradiation, and orbital decompression. Pituitary surgery tried has included total hypophysectomy (Albeaux-Fernet *et al.*, 1955 ; Becker, 1959), stalk section alone and with electrocautery of the pituitary (McCullagh *et al.*, 1958), and implantation of radioactive yttrium into the pituitary (Dogliotti and Ruffo, 1958 ; Molinatti *et al.*, 1959). The results of any form of treatment are difficult to assess because the course of the condition is punctuated with apparently spontaneous exacerbations and remissions. Stalk section alone seems to be less successful than total hypophysectomy, yttrium implantation, or electrocautery with stalk section. We have no experience of pituitary surgery in this condition, but it does seem logical to consider a pituitary approach in any case in which the condition appears to be endangering the patient's sight.

Total Hypophysectomy in Diabetic Retinitis

Young people developing diabetes can usually be kept symptom-free and in good health with insulin. However, with the passage of time it has become obvious that insulin therapy is not the complete answer to this problem and that later complications may develop, including coronary artery disease, diabetic retinitis, and renal damage. It has been suggested that these complications occur earlier if the diabetic control, judged by blood-sugar levels, is indifferent or poor (Keiding *et al.*, 1952 ; Johnsson, 1960). Others have claimed that the control of the diabetes has little or nothing to do with the development of these complications (Dolger, 1947 ; Downie and Martin, 1959). Whatever their cause, there is no doubt that these complications do occur in young people after fifteen or more years of diabetes and that they are extremely distressing. In some cases coronary artery disease or renal disease predominates and results in early death of the patient. If the retinitis progresses more rapidly than the other conditions we are faced with a young patient rapidly going blind. Unfortunately, once the retinitis is marked it usually progresses regardless of measures adopted for improvement of diabetic control.

Poulsen (1953) reported the case of a patient with long-standing diabetes complicated by retinitis who suffered from post-partum necrosis of the pituitary gland. As hypopituitarism developed the insulin requirement fell and the retinitis regressed. Subsequent to this observation Olivecrona and Luft started doing total hypophysectomies in patients with progressive retinitis and other diabetic complications. In an account of the first 20 cases they reported that seven of these patients had died, that hypertension and renal function had improved in the remainder, and that seven showed improvement of vision (Luft *et al.*, 1955). Kinsell (1957) described a series of nine patients ; only three were still alive at the time of his report, and although their vision had improved he considered the operation to be the last resort. In another series of 10 cases, six showed great improvement of vision, but two of these patients and two of the other four died subsequently of hypoglycaemia (Javid *et al.*, 1958). A further 10 cases have recently been reported from Finland. Only one of these patients died ; improvement of vision is claimed in four (Hernberg *et al.*, 1959).

We came to the conclusion that the outlook for a young diabetic faced with blindness is bad enough to justify consideration of this heroic procedure, and we have offered hypophysectomy to a number of carefully selected patients. They have all been of the "juvenile" type with adequate renal function, inulin clearance being greater than 100 ml./minute. The operation has been performed on five patients, the first died eight days post-operatively, and one case is too recent for comment, the results of the other three are shown in Table VI.

TABLE VI.—*Hypophysectomy for Diabetic Retinitis*

Case	Before Operation		Date of Operation	After Operation	
	Insulin	Vision		Insulin	Vision
II	70 u.	6·9 : 6·60	March, 1957	12 u.	6·9 : 6·12
III	90 ,,	0 : 6·60	Oct., 1957	68 ,,	0 : 6·18
IV	76 ,,	0 : C.F.	July, 1958	36 ,,	0 : 6·9

		Before	After
IV	Blood urea, mg. 100 ml.	43	29
	Plasma albumin, g. 100 ml.	3·7	4·1
	Urine protein, g. 24 hrs.	1·1	0·4

The present insulin requirement suggests that hypophysectomy is incomplete in Case III and possibly in Case IV. Fundus paintings of Case II are shown in Fig. 8.

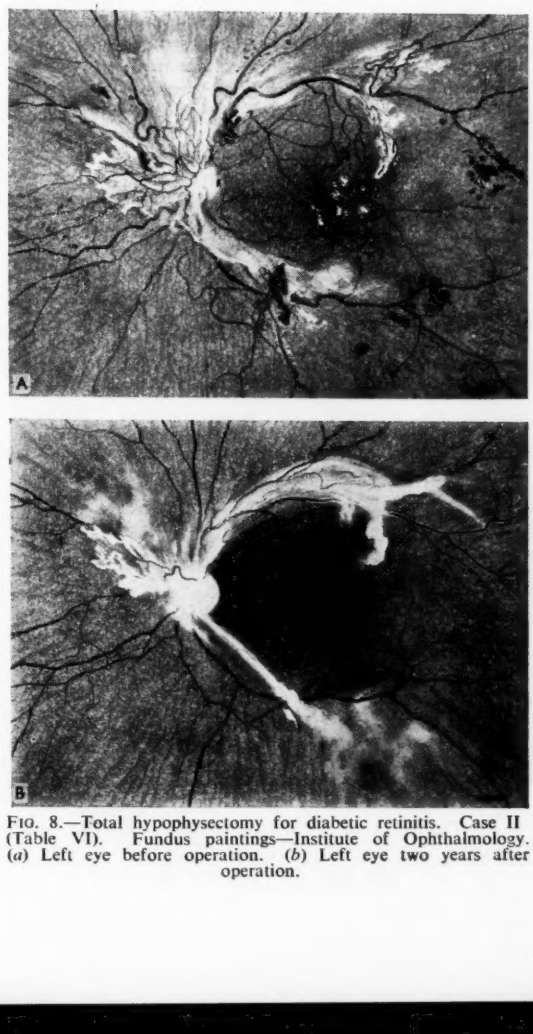


FIG. 8.—Total hypophysectomy for diabetic retinitis. Case II (Table VI). Fundus paintings—Institute of Ophthalmology. (*a*) Left eye before operation. (*b*) Left eye two years after operation.

The operation is a formidable undertaking both for the neurosurgeon and for the physician. It seems that to be of lasting value the hypophysectomy must be complete. Long-standing diabetics are bad risks for intracranial operations and prolonged post-operative unconsciousness and fits are common. The diabetes in the immediate post-operative period is unstable and difficult to control. The development of diabetes insipidus adds to the problems because the osmotic diuresis of glycosuria is greatly exaggerated.

Why hypophysectomy has this effect on the complications of diabetes is not yet clear. The patients receive physiological amounts of adrenal steroid and thyroid hormone after operation ; one therefore suspects that removal of growth hormone is the operative factor. It has been shown that giving human growth hormone to these patients after operation results in hyperglycaemia and ketosis (Greenberg *et al.*, 1958 ; Fankhauser *et al.*, 1959 ; Luft *et al.*, 1959). Vallance-Owen *et al.* (1958) demonstrated on one of our patients that the insulin antagonist present in the plasma albumin of normal people and diabetics disappears after hypophysectomy, but its identity and relation to the complications cannot yet be defined.

Endocrine Surgery in Metastatic Cancer

Total hypophysectomy has been used for the treatment of disseminated cancer of the breast and prostate. Originally it was thought that by removing sources of corticotrophin and gonadotrophin it would have the same effect as oophorectomy and adrenalectomy in lowering the level of circulating oestrogens and benefiting patients with oestrogen-stimulated tumours. Two observations suggest that hypophysectomy does more than this. A proportion of patients who have undergone oophorectomy and adrenalectomy obtain a further remission if hypophysectomy is performed when the condition relapses. We have had two patients in whom objective improvement has been shown in this situation (Fig. 9). The second is that although oestrogen administration will cause an exacerbation of oestrogen-dependent tumours in intact patients or after oophorectomy it fails to do so after hypophysectomy, suggesting that oestrogens are able to stimulate the tumour only in the presence of an as yet unidentified pituitary factor (Pearson and Ray, 1959). Some studies have been made with human growth hormone, but the results so far have been inconclusive (Pearson and Ray, 1959).

A B

FIG. 9.—Carcinoma of breast with multiple bony metastases. Oophorectomy and adrenalectomy in April, 1956. Hypophysectomy in March, 1957. *X*-ray films of femur taken in December, 1956 (A), and July, 1958 (B).

Luft has reported on the results in a series of 59 cases with evidence of remission in 57% of 47 evaluated (Luft *et al.*, 1958). Pearson and Ray (1959) reported remissions in 54% of a series of over 100 cases. It is reasonable to compare the results of adrenalectomy with those from hypophysectomy in general terms, rather than to consider exclusively the effect on the neoplasm. The replacement therapy after adrenalectomy is undoubtedly simpler than after hypophysectomy, but the complete lack of aldosterone after adrenalectomy may lead to the sodium-depletion type of Addisonian crisis. The hypophysectomized patient is not exposed to this hazard, though she has to take thyroid hormone and, in some cases, at least temporarily, pitressin. Schon (1958) has been unable to demonstrate any intellectual or psychological changes after hypophysectomy. It has been our impression that there may be an unexpected euphoria in some cases which, although perhaps beneficial in patients with advanced cancer, has on occasion caused some anxiety. We are doubtful whether it is justified to undertake surgical hypophysectomy in patients with advanced cancer, though it may produce remissions slightly more often than adrenalectomy (Atkins *et al.*, 1957). The current methods of yttrium-90 implantation seem to have advantages over surgical hypophysectomy and bilateral adrenalectomy.

Steroid Therapy

The addition of physiological amounts of cortisone has greatly improved the replacement therapy available for patients with Addison's disease or hypopituitarism. Larger or pharmacological amounts of steroids have been used in the treatment of diseases unrelated to the adrenal gland. Steroids of the cortisone group inhibit the inflammatory reaction of connective-tissue cells, but in many instances the inflammatory reaction is part of the body's defence mechanism and is to be encouraged rather than inhibited. It has, however, become apparent that there are diseases which are really due to the body's reaction being quite disproportionate to the noxious stimulus. The manifestations of the disease are, in fact, those of an exaggerated or inappropriate inflammatory response, and if steroid therapy can inhibit this inappropriate response the manifestations of the patient's disease will be suppressed. The underlying condition is not cured, though it may ultimately burn itself out.

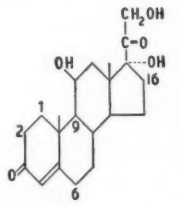
The anti-inflammatory action of steroids is used for this purpose in allergic conditions and diseases like rheumatoid arthritis, rheumatic carditis, disseminated lupus erythematosus, and polyarteritis nodosa. Large doses of steroid will also inhibit antibody production and help in the management of auto-immune conditions like some of the haemolytic anaemias and thrombocytopenic purpuras. Steroid therapy may also be used to suppress the patient's adrenal glands ; the doses required, however, are nearer the physiological levels. This may be

needed in cases of adrenal dysfunction where abnormal androgenic steroids are being made, or in cases of disseminated breast cancer to inhibit adrenal secretion of oestrogens, the so-called medical adrenalectomy.

When large doses of steroids are given for their pharmacological action, the result will be to produce an iatrogenic Cushing's syndrome. There is a tendency to forget that Cushing's syndrome is a serious illness with a grave prognosis—so serious, in fact, that one has no hesitation in advising total adrenalectomy for its treatment. Admittedly, treatment with high doses of steroid may in some situations be life-saving, or produce a temporary remission in an incurable disease. There has been a tendency to overlook the dangers of treatment with cortisone and the newer synthetic steroid hormones and to use them in cases where the treatment may prove more dangerous or disabling than the original disease. It seems likely that many of the complications of steroid therapy are intimately associated with their therapeutic action, but attempts have been made by modifying the steroid molecule to reduce some of the side-effects.

Synthetic Steroid Derivatives

The modified steroids that are now available are shown in Fig. 10. The substitution of a fluorine atom in the 9α position of hydrocortisone leads to a remarkable sodium-retaining action and makes fludrocortisone a useful oral substitute for aldosterone in the replacement therapy of patients with Addison's disease or after adrenalectomy (Garrod *et al.*, 1955). The next development, the insertion of a double bond between carbons 1 and 2, produced an important new series of compounds. The simplest are prednisone and prednisolone, derived from cortisone and hydrocortisone respectively. Therapeutic activity is enhanced five times on a weight basis without any increase of sodium retention (Demartini *et al.*, 1955). With these compounds, steroid therapy can be given at least in moderate doses without any fear of sodium retention, oedema, or hypertension. If very large doses of prednisone or prednisolone are used—more than 50 mg. a day (equivalent to 250 mg. of cortisone)—sodium retention may still occur.



FLUDROCORTISONE	9αfluoro.
PREDNISOLONE	1=2.
6-METHYL PREDNISOLONE	1=2: 6-methyl.
TRIAMCINOLONE	1=2: 9αfluoro: 16αhydroxy
DEXAMETHASONE	1=2: 9αfluoro: 16αmethyl.

FIG. 10.—Modifications of hydrocortisone.

The first modification of prednisolone was 6-methyl prednisolone, which has less sodium-retaining action and slightly greater therapeutic action. It has been claimed to be less likely to produce some of the other side-effects of prednisolone, but it is a little early to be definite about this (McMahon and Gordon, 1958). Triamcinolone has a hydroxy group substituted in the 16-position and a fluorine atom at the 9α position of prednisolone. The sodium-retaining action is completely inhibited in this way, and therapeutic potency is about that of prednisolone (DiRaimondo and Forsham, 1958). Triamcinolone has some side-effects not seen with other steroids—tendency to produce headache, facial flushing, and rather marked anorexia (Hartung, 1958; Kendall and Hart, 1959). The latter may be an advantage because the patient is less likely to gain weight excessively.

The latest modified steroid is dexamethasone. It has enormously enhanced therapeutic potency and very little sodium-retaining action. Why the therapeutic potency is enhanced in this way is not known, but it seems that the degree of enhancement varies from patient to patient. In preliminary studies it was found that on the same moderate dose, 4 mg. a day (equivalent to 150 mg. of cortisone), negative nitrogen balances over a three-weeks period varied from 50 to 150 g. (Slater *et al.*, 1959a). The nitrogen loss can be serious and muscular weakness may occur. The calcium balance became negative because of increased loss in the faeces. In one patient with hypercalcaemia and impaired renal function the plasma calcium rose with dexamethasone, whereas it fell later with prednisone. It had been hoped as a result of animal experiments that dexamethasone would be less likely to cause or aggravate diabetes than other steroids (Arth *et al.*, 1958), but in one patient that we studied no difference could be demonstrated.

Figures for the therapeutic potencies and salt-retaining activities of the various modified steroids are shown in Table VII.

TABLE VII.—*Therapeutic and Sodium-retaining Potencies of Modified Adrenal Steroids*

	Therapeutic Potency	Na-retaining Potency
Cortisone	1	1
Hydrocortisone	1·2	1
Prednisone, prednisolone	5	0·8
6-methyl prednisolone	6	0
16α-hydroxy,9α-fluoro,prednisolone (triamcinolone)	6	0
16α-methyl,9α-fluoro,prednisolone (dexamethasone)	37	0
9α-fluorohydrocortisone (fludrocortisone)	15–20	>100

Dangers of Steroid Therapy

At the present time it seems necessary to emphasize the dangers of steroid therapy rather than to discuss the indications for its use. The following comments are based on 322 patients treated with cortisone, hydrocortisone, and their newer analogues. Of these, 140 received

TABLE VIII.—*Long-term Steroid Therapy. Duration*

6–12 months	in 39 cases
1– 2 years	,, 30 ,,
2– 3 ,,	,, 14 ,,
3– 4 ,,	,, 9 ,,
4– 5 ,,	,, 6 ,,
>5 ,,	,, 6 ,,

TABLE IX.—*Long-term Steroid Therapy. Average Dose in Terms of Cortisone mg./day*

Steroid Used	50–100	100–200	200–400	>400	Total
Cortisone	13	6	5	0	24
Prednisone	27	30	10	3	70
Triamcinolone	2	3	0	0	5
Dexamethasone	1	4	0	0	5

TABLE X.—*Long-term Steroid Therapy. Complications*

Infections (pneumonia 8, joints 2, renal 2, abdomen 3, abscesses 2, encephalitis 1, mycotic aneurysm 1)	19
Osteoporosis—severe	7
Muscle weakness	7
Diabetes { caused	10
Diabetes { aggravated	5
Duodenal ulcer	7
"Cushing's facies"	19
Mental disturbance	1

47 patients did not develop any complications.

physiological doses for Addison's disease, panhypopituitarism, or after adrenalectomy or hypophysectomy, and 78 were given larger doses for less than six months. These are excluded from the following analysis. Of the remaining 104 patients who were treated for more than six months, 30 had collagen diseases and 27 malignant lymphomata and leukaemias. The duration of treatment, the order of dose used, and the complications are shown in Tables VIII, IX, and X.

The most serious side-effects of steroid therapy are associated with infections. Four deaths were directly attributable to treatment and all were the result of infection. The manifestations tend to be suppressed and the patients may be afebrile and feeling well, despite the presence of large abscesses or spreading infection (Beck *et al.*, 1950; Allanby, 1957). Striking examples of this are seen in patients with rheumatoid arthritis developing pyoarthroses (Mills *et al.*, 1957). One patient in this series with disseminated lupus erythematosus and joint-involvement complained of increasing stiffness in the shoulders. Her general condition remained satisfactory, but the joints gradually became swollen and aspiration yielded about 400 ml. of pneumococcal pus from each side. A patient with rheumatoid arthritis developed staphylococcal septicaemia and osteomyelitis of the cervical spine which was detected following the development of neurological symptoms. This patient died, and the other deaths from infection were due to pulmonary aspergillosis in a patient on prolonged steroid therapy for pemphigus; recurrent lung infections aggravated by collapsed thoracic vertebrae due to steroid osteoporosis; and, in one case, to encephalitis occurring during steroid therapy.

Osteoporosis caused symptoms in seven patients; only one of them was suffering from rheumatoid arthritis. Three have had collapsed vertebrae, and in two of these there were troublesome lung infections. One patient, a boy aged 13, developed osteoporosis and renal calculi. Anabolic steroids have been used in an attempt to combat the tendency to osteoporosis (Reifenstein, 1958), but it is not possible to produce objective evidence of their efficacy. Muscle weakness is a well-recognized symptom of Cushing's syndrome, and it is not surprising that it may complicate steroid therapy. Marked weakness occurred in seven patients; in five it followed prednisone treatment and in two dexamethasone. The two who developed weakness on dexamethasone were the patients with the most strongly negative nitrogen balances. It has been suggested that a specific type of myopathy may be produced by triamcinolone (Williams, 1959), but it may well be that the reduction of appetite produced by this steroid accentuates the negative nitrogen balance.

Steroid diabetes developed in 10 cases; this figure is unexpectedly high because some patients were seen in the diabetic clinic after the development of this complication. The diabetes has seldom been severe, though a few patients have had to be given insulin, usually after the development of an infection. Seven patients had trouble with peptic ulceration; these include two in whom an unsuspected periduodenal abscess was found at necropsy and two who bled from their ulcers. Changing to enteric-coated tablets of prednisolone was beneficial in two patients with pain due to duodenal ulceration.

Difficulties may arise as the result of adrenal suppression during prolonged steroid therapy (Salassa *et al.*, 1953). In any severe physical stress, illness, or operation, a considerable increase of plasma hydrocortisone level is needed for maintenance of blood-pressure; this is produced through an increase of pituitary corticotrophin secretion and subsequent increase of adrenal hydrocortisone output. It was originally thought that the defect in patients treated with steroids lay primarily in the adrenal (Larzelere *et al.*, 1957), but it now seems that in some cases the pituitary is at fault and is slow to produce corticotrophin (Holub *et al.*, 1959). Not only is this defective response seen during the course of steroid therapy, but it has been observed for at least two years afterwards (Hayes, 1956). We have had trouble with three patients on this account. One case is of particular interest because it sheds some light on the mechanism.

The adrenal response to corticotrophin is easily tested, but until recently there has been no way of testing the pituitary capacity to produce corticotrophin. One stimulus to increased corticotrophin output is a fall in the circulating level of hydrocortisone. Using the new amphenone analogue 2-methyl-1,2 bis-(3-pyridyl)-1-propanone (SU 4885), it is possible to inhibit the 11-

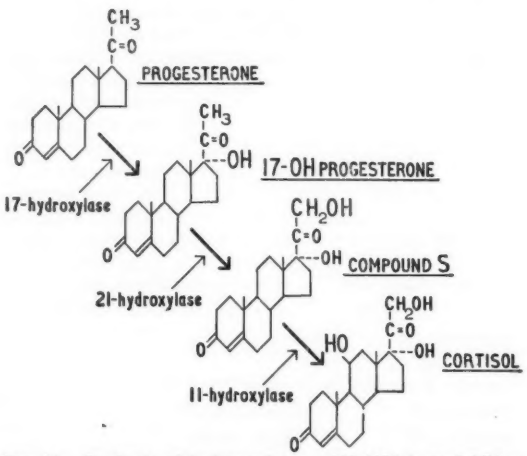


FIG. 11.—Synthesis of hydrocortisone. SU 4885 is an inhibitor of 11-hydroxylase and blocks the last step in hydrocortisone (cortisol) synthesis.

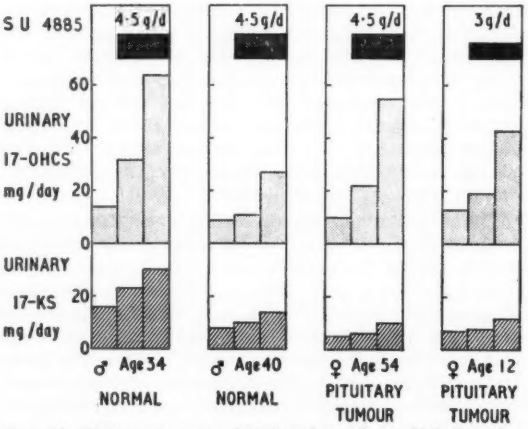


FIG. 12.—Effect of oral administration of an 11-hydroxylase inhibitor (SU 4885) on urinary steroid excretion in four patients with normal pituitary reserve of corticotrophin.

hydroxylation step in the synthesis of hydrocortisone (Fig. 11). The circulating level of hydrocortisone falls, and normally the corticotrophin output rises and the adrenal responds by secreting more 11-deoxyhydrocortisone (compound S) and 17-ketosteroids (Jenkins *et al.*, 1959; Liddle *et al.*, 1959). Hydrocortisone, compound S, and their metabolites are all measured by the standard methods used for estimating 17-hydroxycorticosteroids, and typical responses to SU 4885 in subjects with a normal pituitary reserve of corticotrophin are shown in Fig. 12.

A patient has recently been studied who was having a neck exploration and who had had a short course of steroid therapy five months before (triamcinolone 16 mg./day for six weeks). No steroid cover was given, and twelve hours after the operation there was a period of hypotension responding to intravenous hydrocortisone. Subsequently she showed a completely normal response to corticotrophin but delay in increasing the corticotrophin output (Fig. 13). Similar studies have been reported by Holub *et al.* (1959), Gold *et al.* (1960), and Nelson and Meakin (1960). It appears that in assessing the degree of adrenal suppression after steroid therapy before, for example, a surgical operation, in addition to giving corticotrophin to test the adrenal response, a test of pituitary reserve using SU 4885 should also be undertaken.

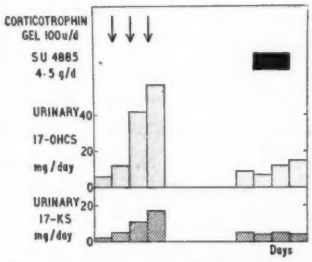


FIG. 13.—Effect of corticotrophin and SU 4885 on urinary steroid excretion in a woman aged 51 with impaired corticotrophin reserve after steroid therapy.

There is one final observation on this series of 104 patients treated with steroids in pharmacological doses for more than six months. Five of the patients have, during or shortly after treatment, developed cancer from which they have died. The details of these cases are shown in Table XI. This may well be a chance finding,

TABLE XI.—*Cancer Complicating Long-term Steroid Therapy*

Age and Sex	Original Disease	Steroid Therapy	Site of Cancer	First Evidence of Cancer	Died
F 46	D.L.E.	June/57–Aug./59	Ovary	Feb./58	Nov./59
M 45	Haemolytic anaemia	Sept./52–June/58	Bronchus	March/58	June/58
F 63	Cranial arteritis	Apr./55–June/56	Duodenum	Oct./57	Dec./58
M 52	Scleroderma	Oct./54–Apr./55 Oct./55–Apr./56	Bronchus	July/57	Feb./58
M 20	Ulcerative colitis	May/53–Oct./55 Sept./57–Mar./59	Bile-duct	Nov./58	March/59

but there are two reasons for drawing attention to it. First, that in published series of cases on long-term steroid therapy there are a number of cases of cancer noted among the "deaths from unrelated causes" (Bunim *et al.*, 1955; Stevenson, 1960). Secondly, there is evidence that carcinomata develop not infrequently in young patients with Cushing's syndrome (Crooke, 1946; Thorne, 1952).

Summary

The two important hormones of the adrenal cortex are hydrocortisone and aldosterone.

The main actions of hydrocortisone are maintenance of blood-pressure and renal function, and the proper distribution of water and sodium in the body fluids.

In severe physical illnesses and surgical operations the circulating level of hydrocortisone must be increased if its function is to be maintained. In some cases the level required may exceed that which the normal adrenal cortex can achieve. The metabolic changes after surgery are not the result of alterations of steroid level although increased hydrocortisone secretion is necessary for the normal metabolic response.

Methods of urinary aldosterone estimation depending on the *p*H 1 extractable fraction are not entirely reliable because this represents a variable proportion of aldosterone secretion in any particular patient.

Aldosterone secretion is often increased in patients with oedema. This appears to be a secondary phenomenon. Blocking the action of aldosterone with the spirolactone compounds may result in a diuresis, even though the aldosterone secretion rate is normal.

Total adrenalectomy has been performed for a number of non-endocrine conditions, including metastatic carcinoma from breast and prostate, malignant hypertension, intractable oedema, and diabetes with complications. Steroid cover for the operation and post-operative replacement therapy are discussed.

There are many unsolved problems concerning the hormones of the anterior pituitary gland, including the extra-adrenal action of corticotrophin and the role of growth hormone in the adult.

The endocrine effects of pituitary-stalk section are described; it is suggested that thyrotrophin but not corticotrophin or gonadotrophin may be secreted in the absence of any vascular connexions between the hypothalamus and pituitary.

The indications for surgical hypophysectomy include metastatic breast cancer, malignant exophthalmos, and progressing diabetic retinitis. In metastatic cancer it is suggested that radioactive yttrium implantation is more suitable than surgical hypophysectomy. The results of hypophysectomy in five patients with severe diabetic retinitis are described.

The new synthetic steroids include prednisone, prednisolone, methyl prednisolone, triamcinolone, and dexamethasone. The main dangers of long-term steroid therapy include infection, osteoporosis, muscle weakness, diabetes, and peptic ulceration.

Attention is drawn to the development of cancer in five patients out of 104 during or shortly after steroid therapy given for more than six months.

Adrenal insufficiency after steroid therapy may be due to delay of corticotrophin release by the anterior pituitary or delay of adrenal cortical response to corticotrophin. Tests with an 11-hydroxylase inhibitor make it possible to detect patients liable to delay of corticotrophin release.

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THE FATE OF THE CLAUDICATOR

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Arterial insufficiency of a limb presents either with pain or with gangrene. The former usually occurs only after exercise—that is intermittent claudication—but may be present at rest. The fate of the gangrenous leg is known ; unless the circulation can be improved by direct arterial surgery or a sympathectomy, amputation is the usual outcome. The prognosis for the claudicator, with or without additional rest pain, is not so well documented, but is more favourable.

The natural history of such patients regarding their arterial disease forms the subject of this investigation. It describes the initial assessment and progress of patients who attended with symptoms and signs of atherosclerotic arterial disease in one or both lower limbs. The patient's doctor was then sent a standard letter which requested information on the patient's survival, the state of the affected limbs, manifestations of atherosclerosis in other parts of the body, and, if applicable, the date and cause of death. Where necessary, details of date and cause of death were obtained from the Registrar-General's records.

Clinical Material

A total of 359 patients were taken at random from the vascular index at this hospital. All were first seen before 1958, to allow for a minimum follow-up period of two years. This represented approximately half of all the patients who attend the vascular clinic during this period. The follow-up period was taken to begin with the first hospital attendance at which a definite diagnosis was made. Diagnosis was based on history and signs of impaired circulation. Incipient or actual gangrene was present in 62 patients. To confirm the clinical diagnosis 205 arteriograms were carried out. Patients thought to have Buerger's disease (thrombo-angiitis obliterans) were excluded, the diagnosis being made on the younger age, the episodic course, the occurrence of attacks of superficial thrombophlebitis, the common localization of the arterial lesions in the distal vessels of upper and lower limbs, and sometimes by arteriography.

There was no other selection of cases, all patients conforming to the above-mentioned criteria being included.

Patients with femoro-popliteal thrombosis and with aorto-iliac stenosis and thrombosis are considered separately. Where applicable, joint figures are presented subsequently.

Femoro-popliteal Thrombosis

There were 250 patients in this group, of whom 222 (87%) were men and 28 (13%) women. The mean age was 58 years (34–81). This age-and-sex distribution is similar to that quoted by many authors (Hines and Barker, 1940; Berry *et al.*, 1955). Diabetes mellitus was present in 16 (8.2%) patients.

Blood-pressure readings were available in 179 patients: 97 (44%) were above 150/90 (Platt, 1959); 119 (54%) were above normal for their age according to Hamilton *et al.* (1954).

Results of Follow-up.—Follow-up was completed on 219 (88%) patients. The diagnosis was made on clinical assessment alone in 105 patients and confirmed by arteriography in another 114. Direct arterial surgery or lumbar sympathectomy was carried out in suitable patients with severe disease (Rob, 1956). The remaining patients were given vasodilator drugs and general advice about the care of their limbs. As the value of the latter measures is uncertain (Semple, 1953), those patients are considered under the heading "Nil" in Table I and subsequently. The mean follow-up period was 37 months. Of 114 patients who received only conservative treatment, 109 were improved or remained unchanged. A further 13 patients required amputation for progressive ischaemia during the period of observation.

TABLE I.—*Results of Follow-up (Survivors)*

	Direct Arterial Surgery or Sympathectomy	Nil	Total
Improved	33 (6)	40 (16)	73
No change	19 (3)	69 (30)	88
Worse	—	5 (2)	5
Total	52	114	166

Figures in parentheses refer to the "other leg" (see below).

"Other Leg" Thrombosis.—Bilateral disease was present from the beginning of observation in 58 patients. One developed gangrene in the other leg during the follow-up period, requiring amputation. The fate of the remaining less-affected limbs is given in parentheses in Table I. There were 57 such limbs. Of these, 46 improved or remained unchanged without surgical treatment. The appearance of ischaemia in a previously normal limb was assumed to be due to arterial thrombosis. Such changes in the "other leg" were noted in 17 patients: 10 had claudication, 2 developed ischaemic ulcers, and 5 required amputation.

Myocardial Ischaemia.—There was evidence of previous ischaemic heart disease in 51 (24%) patients. Of those, 36 had E.C.G. changes of past ischaemia and 15 had a definite history of angina or coronary thrombosis. During the follow-up period a further 51 patients had episodes of myocardial ischaemia; 25 were fatal and 26 non-fatal. Of this group 36% had previous coronary disease, compared with 24% in the whole series. The incidence of raised blood-pressure in this group was about the same as in the whole series.

Cerebrovascular Accidents.—Previous cerebral thrombosis or haemorrhage had occurred in 6 (2.5%) patients. A further 12 (5%) patients were similarly affected during the follow-up period. Of these cases six were fatal and six non-fatal. In this group a previous cerebrovascular accident had occurred in three patients, and raised blood-pressure was present in four.

Mortality during Follow-up Period.—There were 41 (19%) deaths, the causes and distribution of which are given in Table II.

TABLE II.—*Total Number of Deaths in Each Year of Follow-up Period*

	Post-op.	0–1 Yr.	1–2 Yrs.	2–3 Yrs.	3–4 Yrs.	4–5 Yrs.	Total
Coronary thrombosis	1	9	8	6	1		25
Cerebral thrombosis or haemorrhage		2	2	1		1	6
Miscellaneous	3	1		4	2		10
Total	4	12	10	11	3	1	41

Finally, Table III summarizes a number of results of this investigation according to age. The age-groups analysed (45–69 years) comprise 78% of the total follow-up group. The most significant figures in this Table show the greatly increased mortality of patients suffering from peripheral vascular disease.

TABLE III

Years:	45–49	50–54	55–59	60–64	65–69	Total
Total No.	24	36	46	32	33	171
Survivors	23	33	38	26	24	144
Deaths	1	3	8	6	9	27
% Deaths	4	8	17	19	37	Mean 17
Mean survival to death (months)	18	10	29	20	18	Mean 19
Deaths 1,000*	40	80	150	160	370	Mean 170
Registrar-General's deaths 1,000	4·4	7·5	12·5	19·8	31·8	Mean 15.2

* Excluding post-operative deaths.

Aorto-iliac Thrombosis

This group consisted of 109 patients; 94 (86%) were men and 15 (14%) women. The mean age was 53 years (38–77). There were two (2%) patients with diabetes mellitus.

Raised blood-pressure was found in 70 (67%) patients according to Hamilton *et al.* (1954) and was above 150/90 (Platt, 1959) in 51 (49%) patients.

Results of Follow-up.—Follow-up was completed in 103 (94%) patients. The diagnosis was made on clinical signs alone in 12 patients and confirmed by arteriography in 91. The mean follow-up period was 36 months. Table IV summarizes the results during the period of observation. Of 22 patients treated conservatively, 20 were improved or remained unchanged. A further five patients required amputation for progressive ischaemia during the follow-up period.

TABLE IV.—*Results of Follow-up (Survivors)*

	Direct Arterial Surgery or Sympathectomy	Nil	Total
Improved	41 (11)	7 (4)	48
No change	8 (3)	13 (1)	21
Worse	—	2 (1)	2
Total	49	22	71

Figures in brackets refer to the "other leg" (see below).

"Other Leg" Thrombosis.—Evidence of bilateral disease was often found at arteriography and at operation. Only 21 patients had symptoms of ischaemia in both lower limbs at the beginning of the survey. One developed gangrene and required amputation. The fate of the remaining less-affected limbs is given in parentheses in Table IV. Of six patients who received

conservative treatment only, one had increasing claudication. The remaining five limbs improved or remained unchanged. In six patients ischaemia appeared in the previously symptom-free leg: four developed claudication and two required amputation for gangrene.

Myocardial Ischaemia.—Evidence of previous ischaemic heart disease was present in 20 (19%) patients: 15 had E.C.G. changes and 5 had a definite history of angina or coronary thrombosis. During the period of observation there were 20 further episodes of coronary ischaemia, of which 14 were fatal and 6 non-fatal. Of this group, 25% had previous coronary heart disease, compared with 19% in the whole series. Raised blood-pressure was found less often in this group (60%) than in the whole series (67%).

Cerebrovascular Accidents.—Four cerebrovascular accidents occurred during the follow-up period. All were fatal, including the only patient who had suffered a previous cerebral thrombosis. Of this group, two patients had raised blood-pressure.

Mortality During Follow-up Period.—There were 33 (32%) deaths; the causes and distribution are given in Table V. The high proportion of post-operative deaths is due to the greater use of direct arterial surgery in the aorto-iliac group and the magnitude of these operations.

TABLE V.—*Total Number of Deaths in Each Year of Follow-up Period*

	Post-op.	0–1 Yr.	1–2 Yrs.	2–3 Yrs.	3–4 Yrs.	4–5 Yrs.	Total
Coronary thrombosis	5	2	1	2	3	1	14
Cerebral thrombosis or haemorrhage		1	2			1	4
Miscellaneous	7	2	3		2	1	15
Total	12	5	6	2	5	3	33

Finally, Table VI summarizes a number of results of this investigation according to age. The age-groups analysed (45–69 years) comprise 91% of the whole series, and the figures again demonstrate the high mortality of atherosclerotic patients.

TABLE VI

Age:	45–49	50–54	55–59	60–64	65–69	Total
Total No.	20	28	23	17	5	93
Survivors	18	22	13	12	1	66
Deaths	2	6	10	5	4	27
% Deaths	10	21	43	29	80	Mean 36
Mean survival to death (months)	26	29	23	21	26	Mean 27
Deaths 1,000*	50	180	340	290	800	Mean 366
Registrar-General's deaths 1,000	4·4	7·5	12·5	19·8	31·8	Mean 15·2

* Excluding post-operative deaths.

Anticoagulants

We have used long-term treatment with anticoagulants (phenindione) for several years, for reasons that have been similar to those justifying its use after coronary thrombosis (M.R.C., 1959). All patients in this series who had been on continuous anticoagulant treatment from 1957 or earlier were analysed and the results are presented in this section. No specific control group is offered, but the figures for the phenindione series are compared with those of the whole follow-up group, the constitution of the two series being similar. Patients with femoro-popliteal and aorto-iliac disease are presented jointly.

TABLE VII.—*Results of Phenindione Treatment*

	Phenindione Group	"Control"
Improved	69%	51%
No change	26%	45%
Worse	5%	4%
Thrombosis in "other leg"	6%	7%

There were 70 patients in the phenindione group. The figures in Table VII show that there was no significant improvement in the prognosis for the affected limbs as a result of this treatment. Angina or coronary thrombosis developed in 15 (21%) patients during the follow-up period, and was fatal in 6 (40%) cases. The corresponding figures for the whole series are 71 (22%) patients with angina or coronary thrombosis, of whom 39 (55%) died of the latter. Thus, long-term anticoagulant therapy did not reduce the incidence of coronary ischaemia, although the number of deaths due to coronary thrombosis was less.

Discussion

A postal follow-up has obvious disadvantages. However, as the principal complications looked for—gangrene, cardiac or cerebral ischaemia—are all of such a nature that medical aid would be sought immediately, it was thought unlikely that many would have been overlooked. Regarding the severity of claudication, the results were again considered to be accurate enough for the purpose of this survey, especially as there is no intention to prove the value of any particular form of treatment and as replies through an intermediary are probably less subject to observer bias.

Notable among the results are the large number of cases in which leg symptoms remained stationary or were improved without active treatment (180 limbs). Similar results are reported by Hamilton and Wilson (1952), Massarelli and Estes (1957), and DeWolfe *et al.* (1954). On the other hand, Gillhespy (1957) found in his series of femoro-popliteal thromboses that "most untreated patients deteriorated." Similarly, Beaconsfield and Kunlin (1953) write of their aorto-iliac group that "sooner or later bilateral above-knee amputation will be required."

We consider that in many patients intermittent claudication is a relatively benign condition, and that with proper selection only a proportion of patients suffering from this condition will require active surgery. Gangrene will still lead to immediate amputation in some patients, although many limbs can be saved by direct arterial surgery.

Myocardial ischaemia is frequently present in patients with peripheral atherosclerosis, as described by McDonald (1953), Spaulding (1956), and Richards (1957). This is confirmed in the present series, where 71 patients had pre-existing ischaemic cardiac disease and a further 71 episodes of coronary ischaemia occurred during the follow-up period.

The value of long-term anticoagulant therapy is not proved. The figures presented in this survey do not demonstrate any definite improvement due to this measure. A case can be made for continuing the use of long-term anticoagulants in the hope that further results will show an improvement in the prognosis for life and limb.

Summary

219 patients with femoro-popliteal thrombosis and 103 patients with aorto-iliac thrombosis were observed

for an average period of three years after their first attendance at hospital. The results of treatment are analysed, showing that claudication in a large number of patients remained unchanged or improved on conservative treatment only. Angina and coronary thrombosis were common during the follow-up period, and the general mortality of this atherosclerotic group is high. The position of long-term anticoagulant therapy is discussed.

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OBSERVATIONS ON PREVENTION AND DIAGNOSIS OF ANAEMIA IN PREGNANCY

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The high incidence of anaemia in women attending the antenatal clinics of two hospitals in North Staffordshire led, in 1957, to a systematic study, the first results of which have already been published (Giles and Shuttleworth, 1958). They showed that megaloblastic anaemia of pregnancy occurred in at least 2.8% of hospital confinements and that there was almost invariably a good response to folic acid. A megaloblastic bone-marrow, however, was found in only a minority of women who presented with anaemia in pregnancy or the puerperium. In the absence of haemorrhage, iron deficiency accounted for the great majority of anaemias and often complicated a coexistent deficiency of folic acid.

In view of the relatively slight marrow changes in some of the milder cases of megaloblastic anaemia and an unexpectedly high serum iron in a few anaemic women with entirely normoblastic erythropoiesis, those authors surmised that folic-acid deficiency might exist in pregnancy even in the absence of megaloblastic anaemia. That this is in fact the case has now conclusively been demonstrated by Chanarin *et al.* (1958, 1959) by means of tests of folic-acid clearance and absorption.

It was therefore decided to administer folic acid prophylactically to an unselected group of women during the last 11 weeks of pregnancy—not only in order to prevent the onset of megaloblastic anaemia, but also to compare the haemoglobin level at term of women so treated with that of a comparable group of controls.

For several years the prevalence of iron deficiency had convinced us that all antenatal patients need supplementary iron, but the onus for its administration had rested with the family doctor. Since the incidence of iron-deficiency anaemia remained high we felt it advisable that iron should be administered by the hospital to all patients from the time they first attended the antenatal clinic. This new regimen was timed to coincide with the therapeutic trial of folic acid in order to eliminate iron deficiency as a variable factor in the investigation.

Method

From July 1, 1958, onwards all antenatal patients, as soon as they first attended the hospital, were given a daily dose of 540 mg. of ferrous sulphate and 75 mg. of ascorbic acid. They were also handed a sheet of instructions and explanation of why it was necessary that iron and vitamin C should be taken regularly. The medical and nursing staff did their best at every visit to ensure that patients took their iron, and advised them how best to take it. Ferrous sulphate was chosen, since trials of different iron preparations (Kerr and Davidson, 1958) had shown that this, the cheapest of all iron compounds, was quite as effective in raising the haemoglobin level of the great majority of patients as other more expensive iron preparations. Intolerance to ferrous sulphate could often be minimized by the simple advice that the drug be taken during the course of a meal rather than afterwards, which is the common practice. Rather less than 20% of women developed gastro-intestinal symptoms—constipation, nausea, abdominal pain, and, occasionally, diarrhoea; and in such cases other forms of iron, such as ferrous gluconate, "colliron," and ferrous succinate was substituted for ferrous sulphate. A small number of patients (less than 1%), who could not tolerate oral iron in any form, were given a course of injections of intramuscular iron-dextran complex ("imferon"). Ascorbic acid was routinely administered, as it has been claimed (Fisher and Biggs, 1955; Steinkamp *et al.*, 1955) that this vitamin facilitates absorption of iron and reduces some of the side-effects of oral iron preparations.

The selection of patients for the trial of folic acid was based entirely on the order in which they were booked in the antenatal clinic; thus every other patient was given a daily dose of 15 mg. of folic acid from the 29th week of pregnancy onwards. This is undoubtedly far more than the daily needs of a pregnant woman (Lowenstein *et al.*, 1955), but in such a large group of cases, which included many women of rather low intelligence, it was obviously simpler to prescribe an equal number of tablets of three different kinds. Subsequent findings have shown that depletion of folic acid may occur before the 30th week of pregnancy, and our more recent practice is to begin the administration of folic acid at the 26th week.

The haemoglobin of all patients was determined at every visit, and packed cell volumes were estimated and stained blood films examined whenever the haemoglobin dropped below 67% (100% = 14.8 g./100 ml.). At the same time a careful search was maintained for cases of megaloblastic anaemia on the lines of the previous investigation (Giles and Shuttleworth, 1958).

The medical records of all women delivered between October 8, 1958, and October 7, 1959, were then analysed and those treated with folic acid were compared with those who received iron alone. In order to assess the efficacy of prophylactic iron administration in hospital, the control group was also compared with antenatal patients delivered during the year ended June 30, 1958. Only patients who attended the clinic for six weeks or more prior to confinement were included in the final analysis, and women whose gestation terminated before the 37th week were excluded.

The haemoglobin values used in the final comparison were those obtained on the last antenatal visit before delivery. If no haemoglobin estimations were recorded after the beginning of the 38th week of pregnancy, the haemoglobin on the fourth day of the post-natal period was assumed to be a more representative figure, provided that the patient had been delivered naturally and that the recorded loss of blood did not exceed 8 oz. (230 ml.). If neither of these figures was available the case was excluded from analysis.

Effect of Prophylactic Administration of Folic Acid

During the year ended October 7, 1959, 1,479 cases came within the present survey; 758 patients had been treated with folic acid, 721 were controls. The mean haemoglobin level at term of the group treated with folic acid was 82.2% (12.17 g./100 ml.) and that of the controls, treated with iron alone, was 79.82% (11.81 g./100 ml.). The difference of 2.38% has to be compared with a standard error of 0.43, and is therefore statistically highly significant ($P<0.01$).

Fig. 1 compares the haemoglobin levels between the two groups and shows the difference even more clearly than the two mean haemoglobins. The incidence of

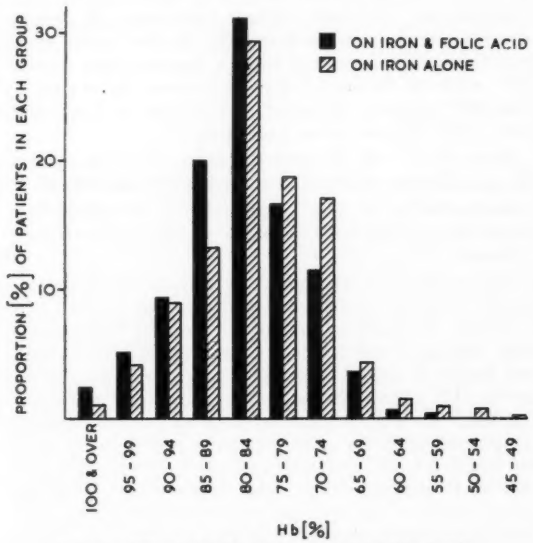

FIG. 1.—Effect of folic acid on haemoglobin levels.

anaemia in the two groups is set out in Table I and suggests not only that moderate and severe anaemia is less common after administration of folic acid, but that the milder cases with haemoglobins between 70 and 80% are less numerous. An analysis of the higher haemoglobin values demonstrates that out of a total of 466 cases with haemoglobins of 85% and above no fewer than 273 (58%) had been treated with folic acid. This confirms the findings of Chanarin *et al.* (1959) that some degree of folic-acid deficiency exists during the latter half of apparently normal pregnancies. The same authors likewise comment on the pronounced folic-acid depletion in normal twin pregnancies. This, too, is reflected in the present series, which includes 26 twin deliveries, 13 in each group; the mean haemoglobin of those treated with folic acid was 82.1% and that of the controls 74.5%. Despite the small numbers, this difference is statistically significant.

TABLE I.—*Anaemia at Term in Cases Treated with Folic Acid and in Controls*

Haemoglobin	Treated with Folic Acid	Controls
Below 80%	33·0%	43·6%
,, 75%	16·3%	24·9%
,, 70%	4·8%	7·5%
,, 65%	1·0%	3·3%
,, 60%	0·3%	1·7%

Columns 2 and 3 give the proportion of patients in each group.

Effect of Routine Administration of Iron

The 721 control cases, treated with iron alone, were compared with 983 antenatal patients delivered during the year ended June 30, 1958, before routine administration of iron in hospital was begun. The latter group of cases included only those in which adequate haematological data were available. The mean haemoglobin at term of these women who had not received iron in hospital was 73.4% (10.86 g./100 ml.), as compared with 79.82% (11.81 g./100 ml.) in the iron-treated group during the current year.

Fig. 2 shows a comparison of haemoglobin levels between the two groups. The reduction of pregnancy

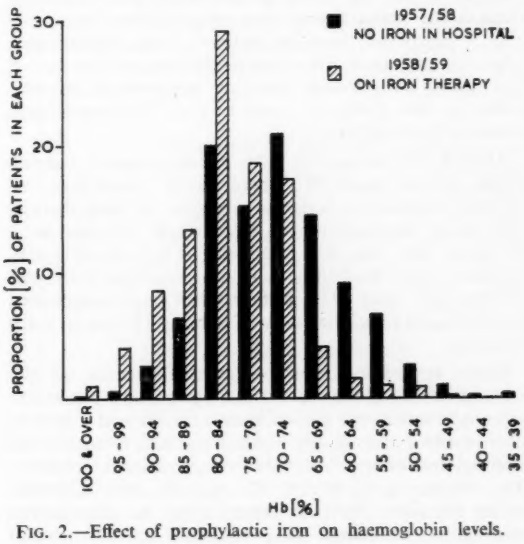

FIG. 2.—Effect of prophylactic iron on haemoglobin levels.

anaemia since routine administration was introduced is strikingly demonstrated. Whereas, in the past, 70% of women were confined with a haemoglobin of less than 80%, the incidence has now fallen to 43%, and haemoglobin values below 70%, which were formerly encountered in 34% of all deliveries, now constitute only just over 7%.

This improvement in the current series was also reflected in the 369 cases in which blood investigations in previous pregnancies were available. In well over 60% of these the haemoglobin during pregnancy and at term was from 5 to 43% higher during the current year than in past pregnancies.

Incidence of Anaemia in Pregnancy and the Response to Treatment

Of the 1,479 patients in the present survey, 978 (66%) had haemoglobin levels below 80% when first seen in the antenatal clinic (Table II). Gatenby and Lillie (1955) have reported a similar incidence.

TABLE II.—*Haemoglobin Levels at First Attendance*

Haemoglobin	No. of Cases
Below 50%	13
50 to 59%	37
60 to 69%	167
70 to 79%	761

After periods varying from six weeks to six months on treatment with iron, with or without folic acid, 595 of these patients went into labour with a haemoglobin of 80% or more. Of the remaining 383, 160 had been treated with folic acid and 223 were controls.

In some of the women who remained anaemic the period of treatment was probably too short, and it is likely that many others did not take the drugs they were given, or at least not regularly. Only in a small number of cases were other conditions recorded which might have explained the lack of response to haematinic drugs—for example, chronic infection and glomerulonephritis. There were doubtless some instances in which low-grade urinary infection was either missed or not recorded.

An interesting observation in at least 80 patients whose haemoglobin remained between 60 and 79% throughout pregnancy was a marked rise, varying from 5 to 20%, in the haemoglobin level after delivery, whereas the mean overall rise after delivery was only 1.5%. Many of these 80 patients had pre-eclamptic toxaemia and some others were delivered of twins. It is tempting to attribute the low ante-partum haemoglobin in this group of cases to true hydraemia with excessive haemodilution.

Among the remaining 303 patients whose haemoglobin did not reach 80% there was a "hard core" of 214 who showed no response whatever to drug therapy and whose haemoglobin at term stayed roughly as it had been when they first attended. It is perhaps significant that only 77 of these had been receiving folic acid and that 137 cases were in the control series, suggesting that folic-acid deficiency may have been a factor in some instances.

There appeared to be no great difference in the haemoglobin levels in the various age-groups, but multiparae who had borne five children or more had a slightly lower mean haemoglobin. After caesarean section the haemoglobin almost invariably dropped quite considerably, averaging 12.4% in 92 patients thus delivered during the year. For this reason alone no post-partum haemoglobin readings were included in the present survey where caesarean section had been performed.

Incidence of Megaloblastic Anaemia

Altogether 66 cases of megaloblastic anaemia of pregnancy have been diagnosed in our hospitals since the first series of 90 cases already published—a total of 156 cases in about three years. Forty-five cases were diagnosed during the period of the folic-acid trial. As shown in Table III, 20 of these derived from patients attending the antenatal clinic, but, as expected (Lowenstein *et al.*, 1955), no cases of megaloblastic anaemia occurred in the group receiving prophylactic folic acid.

TABLE III.—*Incidence of Megaloblastic Anaemia from October 8, 1958, to October 7, 1959*

Type of Case	Antenatal	Post-natal	Total
From the antenatal clinic:			
Treated with folic acid	0	0	0
Controls	16	4	20
Emergency admissions and cases referred direct to laboratory by the family doctor	15	10	25
Total	31	14	45

The incidence of megaloblastic anaemia of pregnancy during the year of the folic-acid trial was 45 in 3,645 deliveries—that is, 1 in 81 hospital confinements, or 1.2%. This compares with a case incidence of 2.8% in 1957–8, as reported by Giles and Shuttleworth (1958) from the same hospitals. Subsequent paragraphs are based on the case records of all the 66 cases diagnosed since the original series was completed.

Clinical Findings.—As in the first series of cases, there was no evidence of any seasonal distribution (Thompson, 1957). The age incidence was likewise similar, the mean age being 29.0 years; 14 patients were primigravidae. About half the patients complained of a sore tongue or ulceration of the mouth, and in 29 cases there had been some degree of anorexia.

Diet.—Although an attempt was made in the antenatal clinic to stress to patients the importance of a good diet, including plenty of animal protein, many women with megaloblastic anaemia still gave a history of an inadequate diet throughout pregnancy. Nearly half of them ate fewer than three meat meals a week.

Degree of Anaemia.—Fewer instances of severe anaemia were encountered than in the first series, only three patients presenting with a haemoglobin below 30%, while in 48 cases it ranged between 40 and 60%. The great majority of patients responded to folic acid with a reticulocyte count exceeding 15%.

Serum Iron.—In 56 cases the serum iron was above 150 μg./100 ml., and in 12 it exceeded 300 μg./100 ml.

Achlorhydria. — The incidence of histamine-fast achlorhydria remained approximately the same as before—namely, 35%.

Fat-absorption.—The faecal fat content and daily fat-excretion on an ordinary hospital diet was estimated in a further 18 cases, a total of 41 patients having now been studied in this way since the original investigation was begun in 1957. The same tests were also carried out in 17 women in late pregnancy who were not anaemic. In Fig. 3, cases as well as normal controls are plotted on a two-dimensional graph showing both the faecal fat concentration and the daily fat excretion. Out of 41 patients, 13 excreted more than 5 g. of fat a day, which is regarded by Frazer (1956) as suggestive of defective fat-absorption; in 14 cases the faecal concentration of fat exceeded 20%. A study of Fig. 3 shows that pregnant women without anaemia tend to excrete much less fat in their faeces than some of the patients with megaloblastic anaemia.

Blood-group Distribution.—After an inquiry by Forshaw (1959), the blood-group distribution in 173 patients with megaloblastic anaemia of pregnancy diagnosed in our hospitals during the past five years

was compared with that of 2,500 random antenatal patients who were not known to be suffering from the disease. The results are seen in Table IV. It shows an apparent increase in the incidence of group A in the

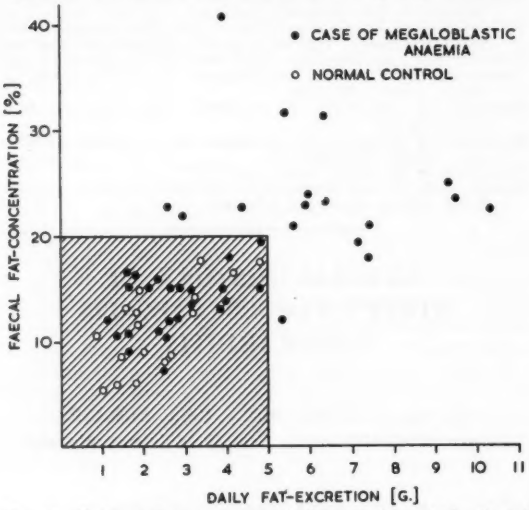

FIG. 3.—Fat-excretion on a normal diet. Values within shaded area are considered normal.

combined series of cases, but the difference is of doubtful statistical significance, and definite conclusions on blood-group distribution must await the analysis of larger numbers of cases. It may be a coincidence that 9 out of 13 patients with megaloblastic anaemia who also showed a raised faecal fat excretion belonged to group A.

TABLE IV.—*Blood-group Distribution*

Blood Group	Megaloblastic Anaemia	Controls
O	43·4%	45·7%
A	49·7%	42·8%
B	4·6%	8·2%
AB	2·3%	3·3%

Discussion

In the past it has been customary to attribute the well-known fall in haemoglobin levels of pregnant women to hydraemia and to accept haemoglobins as low as 67% (10 g./100 ml.) as physiological (Greenhill, 1951; Whitby and Britton, 1957). This view is based on the blood-volume studies by Dieckmann and Wegner (1934) and others, which revealed that, with advancing pregnancy, the increase in plasma volume outstrips a similar increase in the red-cell mass. Since it was shown, however (Benstead and Theobald, 1952; Fisher and Biggs, 1955; Kerr and Davidson, 1958), that a majority of such "physiological" anaemias respond to iron therapy, it has become necessary to revise the definition of pregnancy anaemia (Holland and Bourne, 1955; Camilleri, 1958). In our opinion the haemoglobin of a normal woman in late pregnancy should be at least 80% (11.81 g./100 ml.).

In the present series intensive iron prophylaxis alone has raised the mean haemoglobin at term by 6.4% and has produced an impressive reduction in the incidence of pregnancy anaemia. It would appear that the time has now come for supplementary iron to be issued free of charge to all pregnant women in the way that vitamin preparations have long been made available.

Possibly the most interesting result of the present study has been the obvious benefit derived from the prophylactic administration of folic acid. Not only has it completely prevented the occurrence of megaloblastic anaemia, but it has also raised the haemoglobin at all levels, even in the absence of megaloblastic changes in the marrow. Chanarin *et al.* (1959) have shown that even the normal pregnant woman suffers a relative depletion of folic acid during the last trimester of pregnancy. As might be expected from their findings, the present investigation demonstrates that the haemoglobin level can be raised even in women who by no definition can be called anaemic.

It is clear, however, that deficiency of iron and of folic acid are not the only factors producing pregnancy anaemia. The abrupt rise of haemoglobin levels after delivery in at least 20% of women who remained anaemic despite treatment would seem to show that excessive haemodilution must play a part in some patients with pregnancy anaemia. Fisher and Biggs (1955) noted a similar post-partum rise and came to the same conclusion. The role of infection in the aetiology of anaemia in pregnancy has probably been underrated in the past and will be a subject of further study.

The incidence of megaloblastic anaemia in the present series was 1.2% of all hospital confinements, compared with 2.8% as previously reported by one of us in the same hospitals. This fall is more than could have been expected from folic-acid prophylaxis in the group selected for treatment. Previous workers, including Nichol and Welch (1950), have suggested that ascorbic acid might increase the utilization of folic acid by its reduction to folinic acid. One might therefore conjecture that the lessened incidence among patients not receiving supplementary folic acid is due to the fact that they were treated with large daily doses of vitamin C in addition to iron. On the other hand, without any conclusive evidence that pregnant women commonly suffer from vitamin-C deficiency it would be premature thus to account for the lessened case incidence.

This latest study confirms that an inadequate diet plays an important part in the aetiology of megaloblastic anaemia of pregnancy. It is equally plain that a deficiency of folic acid in the diet is not the sole cause of the disease. Evidence has now been presented which points to an element of malabsorption in a number of cases: 14 out of 41 patients exhibited a much higher faecal fat-concentration or fat-excretion than any of the normal pregnant women who were investigated as controls. If these findings are confirmed in a larger number of cases they might well be explained by latent or mild steatorrhoea, in which megaloblastic anaemia is a well-recognized complication. Since the growing foetus causes a relative depletion of folic acid even in normal pregnancy, a woman with defective intestinal absorption might be expected to develop megaloblastic anaemia in the last trimester. This hypothesis would also explain the recurrence of the disease in subsequent pregnancies.

The blood-group distribution in our series of megaloblastic anaemias is of interest, for an increased incidence of group A is already known to exist in Addisonian anaemia (Aird *et al.*, 1956), but, obviously, further studies are needed to establish a similar blood-group distribution in megaloblastic anaemia of pregnancy.

The present investigation has confirmed that a deficiency of folic acid is very common in late pregnancy, and can readily be prevented by prophylactic administration of this vitamin. The risk of inducing neurological changes in an unrecognized case of Addisonian anaemia, in this age-group and with such a short course of treatment, is exceedingly slight. We therefore have not thought it necessary to add vitamin B_{12} to our prophylactic regimen. Over the age of 30, however, patients with megaloblastic anaemia of pregnancy should be investigated with Addisonian anaemia in mind. In the two hospitals concerned no case has been found in association with pregnancy during the last three years. Francis and Scott (1959) appear to have reached similar conclusions.

Summary

In order to study the routine administration of folic acid during the last trimester of pregnancy, the haemoglobin levels at term of 758 women treated with folic acid and iron have been compared with 721 controls treated with iron alone. The mean haemoglobin in the group treated with folic acid was 82.2%, as against 79.82% in the controls. The difference of 2.38% is statistically significant ($P<0.01$). Folic acid appeared to raise the haemoglobin not only of anaemic patients but also of normal women, resulting in a higher haemoglobin value at all levels.

A comparison of the 721 controls with 983 pregnant women who attended the antenatal clinic before routine iron prophylaxis in hospital was begun has shown a rise in the haemoglobin at term from 73.4 to 79.82%.

66% of women had haemoglobins of less than 80% when they first attended hospital, but in the majority the anaemia responded to treatment even in the control group. In at least 20% of patients who remained anaemic despite treatment there was a sharp rise in the haemoglobin after delivery.

A further 66 cases of megaloblastic anaemia of pregnancy have been reported, 45 of which were diagnosed during the period of the folic-acid trial. There were no cases of the disease in the group treated with folic acid, but the incidence in the control group was also somewhat lower than in the past. The overall incidence was 1.2% of all hospital confinements. In 14 out of 41 cases of megaloblastic anaemia there was evidence of diminished fat-absorption.

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NATURAL HISTORY OF STREPTOCOCCUS FAECALIS ENDOCARDITIS

BY

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Bacterial endocarditis due to *Streptococcus faecalis* has certain distinct features. These must be recognized so that an early diagnosis can be made and effective treatment given. Andrewes and Horder (1906) and Horder (1909) were the first in this country to draw attention to bacterial endocarditis due to this organism. In recent years the importance of this condition has grown because of its resistance to antibiotic therapy. Geraci and Martin (1954) reviewed 33 cases and noted that in 15 there was no underlying heart lesion and that many followed operations on the genito-urinary and gastro-intestinal tracts. They emphasized the high mortality with inadequate treatment. Rantz and Kirby (1943) found that the human infections usually caused by this organism were acute suppurative otitis media, infections of the urinary tract, terminal peritonitis in association with coliform bacillus, and subacute bacterial endocarditis. The incidence of this infection in bacterial endocarditis is variously reported as 3.2% (Sirota *et al.*, 1947), 3.8% (Loewe *et al.*, 1951), and 5–10% (Robbins and Tompsett, 1951). Geraci and Martin (1954) thought that there might have been a relative rise in incidence in the past ten years.

Present Investigation

We here give a review of eight patients with bacterial endocarditis due to *Str. faecalis* (or enterococcus) out of a total of 49 proved cases of bacterial endocarditis admitted to this hospital in the past nine years. In addition, there was one patient with bacterial endarteritis due to this organism. The course of the disease and the problems of treatment are discussed.

Only bacteriologically proved cases are included. Table I gives a list of the various organisms identified. The three cases with a non-haemolytic streptococcus are considered separately because of the different bacteriological properties of that organism and because it is less resistant to penicillin and streptomycin than the average *Str. faecalis*.

TABLE I.—*Organisms Identified in 49 Cases*

Organism	No.	Percentage of Total
Str. viridans	28	57
,, *faecalis*	8	16
Staphylococcus pyogenes	5	10
Non-haemolytic streptococcus	3	6
Pneumococcus	2	4
Bacillus aerogenes	1	2
Str. pyogenes	1	2
,, *agalactiae*	1	2

Bacteriology.—The organism belongs to group 1 of Lancefield's classification. It is usually non-haemolytic. It grows freely in ordinary laboratory media and is heat-resistant. It is usually resistant to penicillin, and may readily develop resistance to other antibiotics. It is a saprophyte in the mouth, intestine, and vagina. In this study each of the strains of *Str. faecalis* conformed to the following characteristics. Morphologically they were Gram-positive oval-shaped cocci, arranged in pairs or short chains. On blood agar their colonies were grey, shiny, and circular. On MacConkey's bile-salt-neutral-red-lactose agar their colonies were small and red, with deep-red centres. The sensitivities of the strains to antibiotics in Cases 2, 3, 4, 7, and 9 were tested *in vitro* by "sentest." The strains in Cases 4 and 7 were apparently sensitive to penicillin and those in Cases 4, 7, and 9 apparently sensitive to streptomycin. These results, based as they are on sentest alone, are not thought sufficient to exclude these strains from the present study. The strains in Cases 1, 5, 6, and 8 were determined by sentest and also by the tube-dilution method. The pattern of their sensitivities to the different antibiotics is therefore much more accurately determined.

Clinical Features.—Table II summarizes the histories of the eight cases of subacute bacterial endocarditis and the only case of *Str. faecalis* endarteritis superimposed upon a traumatic arteriovenous aneurysm. The age incidence varied from 20 to 77. Six of the nine patients were 60 or over, and five of the nine were men. The duration of symptoms varied from 10 days to 24 weeks, the average being 9 weeks.

The source of infection in three patients (Cases 3, 6, and 7) appeared to be in the renal tract, in three patients (Cases 1, 4, and 8) in septic teeth, and in one (Case 2) in a liver abscess. In Cases 5 and 9 no focus of infection was found.

Results of Treatment.—Two patients (Cases 1 and 8) were effectively treated with massive doses of penicillin

TABLE II

Case	Sex and Age	Duration of Symptoms in Weeks	Evidence of Underlying Heart Lesion	Focus of Infection and Portal of Entry	*Str. faecalis* Antibiotic Sensitivity	P.	St.	T.	C.	E.	Antibiotic Therapy	Comment
1	M 68	4	None	Periapical abscess	Slightly Inhibited by	S. 0·1	R. 50	S. <3	<3	—	P. 2–8 mega units daily—5 weeks	Cured
2	M 66	?8	None	Stone in common duct. Cholecystitis liver abscess	Abscess Wound Blood	R. R. R.	R. R. R.	S. R. S.	S. S. S.	— — —	Short courses of i.v. T., C., oral T. P. 1 mega unit and St. 1 g. daily last 3 wks.	Apical systolic murmur developed in hospital. Blood cultures negative while on P. and St. *Died* of cerebral haemorrhage. Necropsy showed vegetations in mitral valve. No stenosis or thickening of chordae tendineae
3	F 64	12	Chorea at 12	Repair of cystocele three months previously. "Edentulous"	1st admission 2nd admission—relapse	R. R.	R. R.	S. S.	S. S.	S. —	P. 2 mega units and St. 2 g. daily 1 week. T. 1·5 g. daily for 8 wks. P. 8 mega units, St. 2 g.→1 g., and probenecid 2 g. daily for 8 wks.	No response initially. Blood sterile while on tetracycline. Clinical improvement. Relapse 1 month later. *Cured* with P. and St. Moderate deafness and dizziness
4	M 77	12	Harsh apical systolic murmur 6 months previously	Dental sepsis		S.	S.	S.	S.	—	P. 8 mega units, St. 2 g., and probenecid 1·5 g. daily for 7 wks	*Cured.* Heart signs unchanged
5	F 34	?12	Mitral stenosis. Aortic stenosis and incompetence	Teeth healthy. No focus found	Resistant to Inhibited by	R. — 6	R. >50 —	S. — <3	S. — 6	— — —	P. 4–8 mega units, St. 2–1 g., and probenecid 2 g. daily for 8 wks	Infection apparently cured. Slight vestibular damage. *Died* of congestive cardiac failure 5 wks later. No necropsy
6	M 60	4	None	Removal of ureteric calculus 4 months previously	Urine Blood Inhibited by	R. R. 6	R. R. 50	S. S. <3	R. S. 6	— — —	P. 4–16 mega units and St. 4 g., daily for 5 wks. Chlortetracycline 2 g. for 2 wks	Developed gross aortic incompetence. Infection apparently cured. *Died* 5 months later of congestive cardiac failure. No necropsy
7	F 53	3	Previous mitral valvotomy. Mitral stenosis. Aortic stenosis and incompetence	Pyelonephritis 3 wks previously. "Edentulous"		S.	S.	S.	S.	—	P. 4 mega units St. 2 g., and probenecid 2 g. daily for 6 wks	Infection apparently cured. Slight vestibular damage. Aortic incompetence worsened. *Died* 6 wks later. Necropsy showed small vegetation on anterior aortic cusp (? sterile) and perforation of cusp
8	M 20	1½	Aortic incompetence. Mild mitral stenosis. Previous subacute bacterial endocarditis due to *Str. viridans*	Erupting tooth with infection	Inhibited by	S. 0·05	R. 50	S. <3	S. 3	— —	P. 4 mega units daily for 6 wks	*Cured.* Aortic incompetence worsened
9	F 60	24	Normal heart. Traumatic arteriovenous aneurysm of right common carotid artery after mastoidectomy	No focus found. "Edentulous"		R.	S.	S.	S.	—	St. 2–1 g. daily for 4 wks. Oral P. V 3 g. daily 4 wks after	*Cured.* Slight vestibular damage, recovering subsequently

P. = Penicillin. St. = Streptomycin. T. = Tetracycline. C. = Chloramphenicol. E. = Erythromycin. R. = Resistant. S. = Sensitive.
The sensitivity tests were performed by either the Evans sentest technique or the tube-dilution method. The "edentulous" state was purely a clinical observation. Penicillin concentrations are expressed in units per ml. Streptomycin, tetracycline, and chloramphenicol concentrations are expressed in μg. per ml.

alone, and two (Cases 3 and 4) with the combined regime of penicillin and streptomycin. The case of bacterial endarteritis was cured by streptomycin and oral penicillin. Case 3 responded to oral tetracycline clinically, and bacteriaemia was suppressed during therapy, but she relapsed a month after treatment. She was subsequently cured with combined penicillin and streptomycin.

Deaths.—Four of the nine patients died. Three deaths occurred 5, 6, and 20 weeks after the end of apparently successful treatment, and were from congestive heart failure. The fourth died from cerebral haemorrhage while being treated.

Illustrative Cases

The following case summaries illustrate a number of interesting points.

Case 2.—A man of 66 had no significant past history apart from a minor stroke 12 months previously. He was admitted to hospital with typical biliary colic and was treated conservatively. Two months later he was readmitted with obstructive jaundice. At laparotomy a stone was found in the common bile-duct. The gall-bladder was inflamed. An abscess found in the right lobe of the liver was drained and *Str. faecalis* isolated. He was treated with intravenous tetracycline for two weeks and oral neomycin for two days. The jaundice subsided. He remained anaemic and unwell, and developed a bedsore from which *Str. faecalis* was isolated. A low-grade pyrexia persisted. Transfusion and a course of chloramphenicol were given with temporary improvement. At this stage, some three months after admission, *Str. faecalis* was isolated from a number of blood cultures. It was resistant to penicillin and streptomycin and sensitive to the broad-spectrum antibiotics *in vitro*. An apical systolic murmur was heard for the first time. Tetracycline was given for two weeks, but bacteriaemia persisted. Combined therapy with penicillin and streptomycin sterilized the blood-stream, but the patient died suddenly of a cerebrovascular accident three weeks after the beginning of treatment. At necropsy vegetations were found on the mitral valve, which showed no evidence of previous rheumatic disease.

Comment.—Clearly the focus of infection here was the biliary tract and liver. The bacterial endocarditis appeared to have developed on a normal valve. Blood cultures remained positive while the patient was receiving tetracycline.

Case 6.—A dental surgeon of 60 had previously had regular medical examinations, which revealed no evidence of valvular disease. Four months previously a ureteric calculus had been removed in another hospital, to which he was later readmitted with malaise, vague pains, and transient loss of vision. On examination, an apical systolic murmur was noted; E.S.R. was 40 mm. per hour (Westergren). Coliform bacilli and *Str. faecalis* were isolated from his urine, and the latter organism was also cultured from his blood. A course of streptomycin, 2 g. daily, was given for a week, the treatment being continued at home with chlortetracycline for two weeks. He remained unwell. On admission to this hospital he was found to have aortic incompetence, splenomegaly, and anaemia. *Str. faecalis* was again isolated from the blood-stream. It was resistant to penicillin and streptomycin, and sensitive to tetracycline and chloramphenicol *in vitro*. Massive doses of penicillin, increasing from 4 to 16 mega units daily, with 4 g. of streptomycin, reducing to 2 g. daily, appeared to control the infection. Repeated blood cultures were sterile. However, he developed mild vertigo and died from congestive cardiac failure five months after the cessation of antibiotic therapy.

Comment.—In this case the subacute bacterial endocarditis followed a urological operation. Delay in diagnosis with inadequate initial antibiotic treatment had unfortunate results. Mitral and aortic incompetence were apparently caused by infection superimposed on normal valves. Although the infection was successfully controlled, the heart failure progressed and was the cause of death.

Case 3.—A housewife aged 64 had chorea as a child and repair of cystocele three months prior to admission. No heart murmur was recorded then. Ever since the operation she had felt unwell, with vague pains and a low-grade fever. On admission she was found to have mild pyrexia, mitral incompetence, splenomegaly, raised E.S.R., and a mild normochromic anaemia. Urine culture was sterile. *Str. faecalis* was isolated from the blood-stream in repeated cultures. It was resistant to penicillin and streptomycin and sensitive to all broad-spectrum antibiotics. Two mega units of penicillin and 2 g. of streptomycin given daily for a week had no effect. Bacteriaemia persisted. She was given 1.5 g. of oral tetracycline daily for eight weeks with clinical improvement and suppression of bacteriaemia, but the infection relapsed a month later. This time she was given 8 mega units of penicillin intramuscularly with 2 g. of probenecid orally and 2 g. of streptomycin daily for two months with complete cure. She was well four months later and blood cultures remained sterile, though a moderate degree of eighth-nerve damage persisted.

Comment.—This case underlines our opinion that broad-spectrum antibiotics should not be used by themselves in this condition, even though the organism is sensitive to these drugs. Moreover, failure to respond to relatively normal doses of penicillin and streptomycin should not tempt one to abandon this regime, but emphasizes the need for much higher doses of these antibiotics until response is achieved.

Discussion

The recorded incidence of this form of bacterial endocarditis varies from 3% to 10%. It occurred in 16% of 49 cases in the present series. The peak incidence in men has been said to occur at about 60 years and in women at about 30. This corresponds with the age when men suffer from urological disorders and with the peak incidence of abortions in women.

The precipitating factors are many and varied. The association of this form of endocarditis with oral infection, such as a periapical abscess, though uncommon, has been recorded (James, 1952; Geraci and Martin, 1954). The urinary tract is by far the commonest focus of infection in most cases. This is not surprising in view of the high frequency of positive cultures of *Str. faecalis* from the urine of patients with infections of the urinary tract. It is interesting to note that transient bacteriaemia has been said to occur in 45% of patients who have had transurethral resections (Creevy and Feeney, 1949). Merritt (1951) reported a rather high incidence of 8% of bacterial endocarditis after transurethral resection in 7,000 cases. The precipitating factors in the four cases of *Str. faecalis* endocarditis reported by Finn and Kane (1952) were prostatectomy, urethral dilatation, and removal of a renal calculus. In two of the three cases recorded by Cates *et al.* (1951) the endocarditis followed abortion and prostatectomy respectively. Beattie (1954) reported two cases—one after forceps delivery and one after prostatectomy.

In Cases 3, 6, and 7 in our series the infection followed repair of cystocele, removal of renal calculus, and pyelonephritis respectively. The gastro-intestinal tract seems to have been less frequently incriminated. McCoy and Mason (1951) described a case associated with carcinoma of the sigmoid colon. They postulated

that the malignant ulcers might have been the sites of entry of the organism. The infection has also been known to follow haemorrhoidectomy (Geraci and Martin, 1954). In Case 2 in this series it followed ascending cholangitis and liver abscess. Our observations bear out the experience of others that this form of bacterial endocarditis may follow gynaecological and urological procedures, gastro-intestinal infections, and dental sepsis. An edentulous state is therefore no bar to the diagnosis of subacute bacterial endocarditis, because the focus of infection may be at any of the other sites mentioned and because there may be infected buried roots.

Bacterial endarteritis superimposed on an arteriovenous aneurysm is well known. Parmley *et al.* (1954) described the only case of endarteritis and endocarditis due to *Str. faecalis* complicating a traumatic femoral arteriovenous aneurysm. Our Case 9 had apparently had the infection for six months without evidence of endocarditis.

The percentage of patients with previously normal hearts is varyingly reported as between zero (Sirota *et al.*, 1947) and 55 (Geraci and Martin, 1954). Three of our eight cases had apparently normal hearts. The ability of this organism to settle on normal endocardium is difficult to explain.

It has been stated (Geraci and Martin, 1954) that suppurative lesions are not uncommon in this condition. Horder (1909) described a case complicated by a splenic abscess which ruptured, causing general peritonitis. Rantz and Kirby (1943) had a similar case and two others, one with an abscess in the myocardium and one with ulceration of the interventricular septum. None of our cases had evidence of peripheral suppurative lesions.

The sensitivity of the organism to antibiotics should be tested in every case. Table III (modified from Robbins and Tompsett, 1951) compares the sensitivity of *Str. faecalis* to penicillin with that of the other common streptococci.

TABLE III

Organism	Inhibitory Concentration of Penicillin
Str. faecalis	Usually greater than 1 unit ml.
,, *viridans*	0·02 to 0·03 unit ml.
,, *pyogenes*	0·02 or less ,,

Sirota *et al.* (1947) stated that the average *Str. faecalis* was about 36 times as resistant to streptomycin compared with the standard organism. There is, however, no direct correlation between the sensitivity results and the outcome of antibiotic therapy, as illustrated by Case 3. Occasionally the organism may turn out to be relatively sensitive to penicillin (see Cases 1, 4, 7, and 8); though unusual, it has been recorded (Mathews, 1948; McCoy and Mason, 1951).

Combined penicillin and streptomycin therapy was first advocated by Hunter (1947), and its value was subsequently confirmed by Robbins and Tompsett (1951), Cates *et al.* (1951), and Geraci and Martin (1954). Cates *et al.* (1951) further demonstrated in the laboratory that the effect of the combination was not purely additive, but synergistic. Our results agree with those of these authors. The dosage of antibiotics recommended by Hunter is 10 mega units of penicillin and 2 g. of streptomycin daily for a minimum period of six weeks. In certain instances, 4 g. of streptomycin daily may be necessary initially to achieve response. 2 g. of probenecid daily by mouth should be added if the organism is extremely insensitive to penicillin.

Hager *et al.* (1951) successfully treated a case with 5 mega units of penicillin and 24 g. of caronamide daily. The serum level of penicillin was found to be increased twentyfold. In Geraci and Martin's series seven of the treated patients (22%) were cured by penicillin alone. Our Cases 1 and 8 were successfully treated with large doses of penicillin alone. Chlortetracycline has proved disappointing (Brainerd *et al.*, 1949; Harvey *et al.*, 1949). There have been very few reported cures from its use. Waisbren (1954) recorded a case cured by the combination of erythromycin, chlortetracycline, and streptomycin, and suggested this regime as an alternative when penicillin and streptomycin had failed. Havard *et al.* (1959) reported a case in which the organism was extremely resistant to streptomycin and to the combination of penicillin and streptomycin tested *in vitro*. Cure was achieved by the use of systemic penicillin and neomycin, though transient renal damage was produced and the patient became totally deaf.

Prolonged treatment with streptomycin often causes eighth-nerve damage. In such a lethal disease it is a calculated risk which must be taken. Renal function should always be determined, and, if impaired, streptomycin should be used with greater care.

The recorded results of treatment are difficult to evaluate, since the outcome depends not only on the cure of the infection, but also on an early diagnosis and on the presence or absence of heart failure. Using penicillin and streptomycin in early cases, Geraci and Martin had a mortality of only 14%.

Antibiotic cover should be given to patients with rheumatic or congenital heart lesions when undergoing gastro-intestinal, gynaecological, urological, or dental operations. There is no evidence to suggest that in the case of dental operations the usual regime of penicillin cover is inadequate. For the other procedures we recommend 2 mega units of penicillin and 1 g. of streptomycin daily, given immediately before the operation and for three days subsequently. Although the risk of bacterial endocarditis developing after dental operations is well recognized, the risk after other types of surgery is rarely appreciated.

Summary

Eight cases of subacute bacterial endocarditis and one case of bacterial endarteritis due to *Str. faecalis* are analysed. The ability of this organism to settle on a normal heart is stressed and the various precipitating factors are discussed. Combined therapy with large doses of penicillin and streptomycin, with or without probenecid, is recommended. Experience to date suggests that the broad-spectrum antibiotics should rarely be used by themselves in this condition. A regime of prophylaxis is recommended for patients with rheumatic or congenital heart lesions undergoing certain operations.

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AORTIC OCCLUSION (LERICHE'S SYNDROME) IN MITRAL STENOSIS

REPORT OF SIX CASES

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Sudden occlusion of the aortic bifurcation by a "saddle" embolus is an uncommon, but well-recognized, complication of mitral stenosis. It usually presents as an acute surgical emergency (Lodin *et al.*, 1955). Peripheral emboli are a more frequent hazard to the patient with mitral stenosis and auricular fibrillation. Gradual occlusion of the abdominal aorta leading to a typical Leriche syndrome does not seem to have been described as a complication of mitral stenosis. This syndrome is characterized by bilateral intermittent claudication, wasting and weakness of the muscles in the lower limbs, and, in the male, loss of sexual potency. Mild nutritional disturbances of the skin may also be noted. Gangrene is a late and surprisingly uncommon complication. Before our previous paper (Starer and Sutton, 1958) none of the recent larger series on insidious aortic thrombosis mentioned mitral stenosis as an aetiological factor (Milanés *et al.*, 1952; Beaconsfield and Kunlin, 1953; DeBakey *et al.*, 1954; Pataro *et al.*, 1954).

In the diagnostic radiological department at St. Mary's Hospital six patients have been seen during the last few years in whom a typical Leriche syndrome developed during the course of mitral stenosis with auricular fibrillation. These cases have occurred among some 60 patients with aortic thrombosis, 32 of which were reported in some detail in our previous communication (Starer and Sutton, 1958). However, only passing reference was made in that article to the aetiological significance of mitral stenosis, and the evidence is now presented in more detail.

Case 1

This patient had rheumatic fever in 1931, when aged 23. During 1941 she became short of breath and developed swelling of the ankles. From 1947 onwards she had several episodes of left submammary pain with cough and frothy sputum. In 1948 her right arm suddenly became white and cold. She felt pain in the arm when she used it vigorously; this pain was relieved by rest. Gradually the symptoms abated. During 1953 she was confined to bed for a few days with a mild gastro-intestinal upset. On rising she noticed coldness of both legs, gradually creeping up to the knees. This gave way to pain and later to numbness, and her toes became blue. On admission to her local hospital both femoral arteries were found to be pulsate. Her condition improved, but two weeks later the femoral pulses could no longer be felt and walking was limited to 50 yards (45.7 metres) because of bilateral claudication.

On admission to St. Mary's Hospital on December 31, 1953, signs of mitral stenosis and auricular fibrillation were observed. No pulses could be felt in the right brachial artery or at the wrist, and no pulses were palpable in the lower limbs. B.P. was 150/100 mm. Hg. No nutritional changes were present in the legs.

Aortography showed complete occlusion of the lower abdominal aorta (Fig. 1).

On February 3, 1954, valvotomy was performed. The auricle was moderately enlarged and contained a single clot. The degree of stenosis was slight, the valve easily admitting an index finger.

Comment.—From the present point of view this case is of particular interest. After undoubted peripheral emboli in both legs the femoral pulses disappeared during observation in hospital without, apparently, any further embolic episodes.

FIG. 1.—Case 1. Complete occlusion of the lower abdominal aorta opposite L 3.

Case 2

In 1936, at the age of 34, this patient had an attack of rheumatic fever. Nine years later she began to complain of shortness of breath on exertion. One morning in 1945 she awoke from sleep to find both legs numb and cold. Two days later she experienced severe pain in the buttocks, thighs, and legs. The feet became cold and blue. On attempting to walk, pain in the lower limbs immediately became worse, but some pain persisted at rest. Gradually this improved until she could walk 50 yards.

Examination on July 1, 1954, showed her to have mitral stenosis and auricular fibrillation. No nutritional changes were observed in the legs, though the feet were cold to touch. No pulses were palpable in the lower limbs.

A percutaneous lumbar aortogram showed occlusion of the aorta beginning at the level of the inferior mesenteric artery; its lower limit was at the common iliac bifurcation on the right but well down in the thigh on the left.

Comment.—In this patient, also, maximal development of symptoms occurred over a period of several days, during which there was no evidence of acute aortic embolization.

Case 3

This patient, a woman aged 45, had rheumatic fever at the age of 9. She remained well until she was 31, when she had a sudden onset of pain in the right leg; this was made worse by exercise and relieved by rest. After a short time the pain disappeared. When 42 she suffered a cerebral embolus, causing temporary loss of consciousness and transient left-sided hemiparesis; she made a perfect recovery from this. Six months later she suddenly developed pain in the right foot, gradually spreading to both legs. It was aggravated by exercise, walking being limited to 100 yards (91 metres). By this time she was also complaining of increasing shortness of breath, and mitral stenosis with auricular fibrillation was diagnosed. At the age of 44 a mitral valvotomy was performed elsewhere, with marked relief of dyspnoea.

An aortogram performed at St. Mary's Hospital showed occlusion of the aorta from just below the level of the renal arteries. The lower limits of the block were difficult to define, but both femoral arteries filled faintly.

Comment.—Here again the full development of symptoms occurred gradually after an embolus into the right leg.

Case 4

This patient began to complain of increasing shortness of breath in 1942, when she was 29. Eight years later this had become disabling and mitral stenosis was diagnosed. During the next year (1951) auricular fibrillation was first noted. In 1952, while having a bath, she experienced sudden cramp in the right leg and temporary loss of power in that limb, which also became white and cold. She gradually recovered over the next few weeks, but was left with pain in the calf on exercise. In the following year, while convalescing from lobar pneumonia, she suffered a similar episode involving the left leg. Since then she has had cramp in the left calf, both thighs, and hips on walking, her walking distance being reduced to 15 yards (13.7 metres). The cramp is eased by rest, but she also has it during the night. The legs and thighs became very thin, and she suffered from persistent backache. There was marked weakness of the legs.

On examination the presence of mitral stenosis and auricular fibrillation was confirmed. B.P. was 110/85 mm. Hg. There was marked wasting of both legs and thighs, and the feet were cold. Pulses could not be felt in the legs, but there were no nutritional disturbances.

Two aortograms were carried out. The first (in 1952) between the two embolic episodes, demonstrated obstruction of the right common iliac artery only. The second aortogram (on July 2, 1954, after the second embolus, when symptoms were fully developed) showed complete obstruction of the lower abdominal aorta and common iliac arteries,

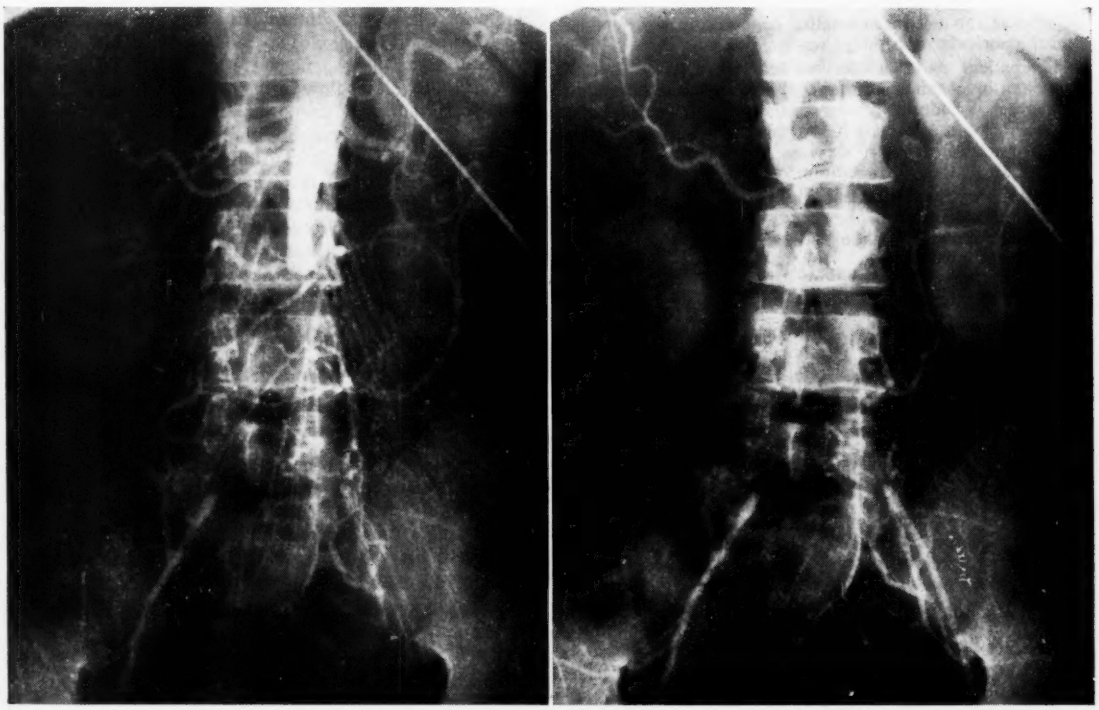

FIG. 2.—Case 5. Serial films from aortogram showing complete occlusion of the aorta opposite L 3. The lower limits of the block are at the iliac bifurcations. The upper pole of the right kidney shows evidence of old infarct.

and on the left there was probably a separate popliteal block. In February, 1954, valvotomy was performed. The auricular appendage was unusually large, but no clot was present. The valve orifice was estimated at 1.5 sq. cm., and a good split was obtained. She made a good recovery from her operation, but walking was still limited by claudication. Two years later there was no change in her condition.

Case 5

As a child this patient, a man aged 37, had three attacks of rheumatic fever. During the war he was rejected from military service because of mitral stenosis, and at that time began to suffer from occasional shortness of breath. In 1948, at the age of 32, he had two attacks of cerebral embolism, both causing transient left hemiplegia. He was admitted to St. Mary's Hospital and found to have auricular fibrillation. Recovery was rapid and complete. In 1949 he had the first of a series of embolic episodes in the lower limbs. They were associated with sudden pain, coldness, and numbness of the legs, with return to normal in about two weeks. Gradually, however, he began to complain of intermittent claudication. Eventually, by 1953, he was left with severe bilateral claudication, numbness over the coccyx, and impotence.

On admission to hospital in August, 1953, the presence of mitral stenosis and auricular fibrillation was confirmed. B.P. was 120/66 mm. Hg. A minimal left hemiparesis was present. The legs and buttocks were wasted, the feet were cold, but no nutritional changes were noted. No pulses could be felt in the lower limbs.

An aortogram showed complete occlusion of the aorta, extending from the lower border of the third lumbar vertebral body to the bifurcations of the common iliac arteries on both sides. Above the upper limit of the block the aortic lumen was narrowed up to the level of the renal arteries. There was also evidence of old infarction of the upper pole of the right kidney (Fig. 2).

In October, 1953, mitral valvotomy was performed (Mr. Lance Bromley). The auricular appendage was moderate in size, and no clot was present in the auricle. The mitral orifice was about 1 cm. in length. A good split was obtained, and the auricular appendage was amputated.

The patient made an excellent recovery. Because of the danger of involvement of the renal arteries in the thrombotic process, it was decided to graft the aorta. An operation was carried out in April, 1954 (Professor Rob). A freeze-dried arterial homograft was inserted. Unfortunately the patient died after the operation.

Post-mortem examination showed the cause of death to have been leakage from the graft above the aortic bifurcation. The remaining aorta and other great vessels showed no evidence of atheroma.

Case 6

This man, aged 49, had been perfectly well until three weeks before admission, when he experienced pain in the left calf of sudden onset, beginning during exercise. It was followed by pins and needles in both feet. During the next few days the left foot became colder than the right, and he began to complain of pain in the calves on walking. This was relieved by rest. There was no history of rheumatic fever, and heart disease had not been previously diagnosed.

On examination he was found to have auricular fibrillation and the classical signs, clinically and radiologically, of mitral stenosis. No pulses could be felt in the lower limbs. The feet were cold, but no nutritional skin changes were present. No abnormal neurological signs were elicited, and no convincing evidence of muscle wasting was noted.

Aortography showed occlusion of the abdominal aorta from the level of the third lumbar vertebra, the block extending to the common iliac birfurcations on both sides. The collateral circulation was not as abundant as is usually seen in cases of aortic occlusion, possibly because the lesion was very recent.

Discussion

It is clear from consideration of the case-histories that the patients presented in this series had in fact suffered from peripheral emboli and that the subsequent development of occlusion of the abdominal aorta was related to these. It is equally clear, however, that these were not "saddle" emboli remaining impacted at the aortic bifurcation. After the original peripheral emboli the subsequent course of events which led to aortic occlusion is not clear. Two possibilities require consideration.

The first is that an extensive thrombosis involving the aorta was built up by the accumulation of repeated small emboli, most of which were too small to produce major symptoms by themselves. The patients under review here did in fact give histories of multiple emboli. More may have occurred which were too small to give rise to immediate symptoms but which finally led to the established picture of aortic occlusion.

The second possibility is that there was progressive clotting in the vessel proximal to the peripheral embolic occlusion. This may have occurred slowly and have led eventually to the Leriche syndrome. When clot becomes impacted in a vessel the flow of blood distally and proximally ceases, and this favours thrombosis in the stagnant segments. As a collateral circulation develops the blocked vessel becomes filled in its more distal portions by retrograde flow through collaterals. Thrombosis will spread distally to the mouth of the nearest important collateral. The resulting appearance can readily be seen on arteriograms. Proximal spread of thrombosis continues for the same reason. In the case of the common iliac artery, a swift flow is encountered again at the aortic bifurcation; nevertheless, clot is able to build up along the wall of the aorta—a state of affairs than can also be observed in aortograms. Hence, clot spreads or is carried down the opposite iliac artery. Once both common iliac arteries are occluded blood-flow in the lowermost aorta becomes greatly diminished, the only effluents being relatively small vessels. Thrombosis is again favoured and continues up to the level of the renal arteries. These vessels are large and receive a large volume of blood, and flow in the aorta above that level is again considerable. It is presumably for this reason that thrombosis commonly stops at the level of the renal arteries. Some evidence for this hypothesis can be found in the literature. Baldwin and Thomas (1954) describe a case of spreading thrombosis after an embolus, and Burt *et al.* (1955) also discuss emboli as a source of spreading thrombosis.

On present evidence it is not possible to be certain which of the views discussed here is likely to be correct. It could also be argued that patients with mitral stenosis and auricular fibrillation have an increased liability to thrombosis either as a result of changes in the blood or because of their abnormal circulatory dynamics. This is certainly true of the pulmonary circulation, where these patients are liable to spontaneous thrombosis.

If any undue tendency to thrombosis does exist, it would favour the propagation of clot, though such assumption is in no way necessary for our thesis.

The course of events in these patients may be further illustrated by the following case history.

Case 7.—A spinster aged 62 was confined to bed for 14 days with an attack of gastro-enteritis. On getting up

she noticed her right leg to be numb, and, when she attempted to walk, found that she was unsteady because of weakness of both legs. She had been getting increasingly short of breath in recent months, but was not known to have suffered from heart disease. On admission she was found to have auricular fibrillation and signs of mitral stenosis. B.P. was 180/90. The femoral pulses could not be felt on either side. An aortogram showed occlusion of the left common iliac artery at its origin, the lower limit of the block lying near the origin of the external iliac artery. On the right side the external iliac artery was occluded above Poupart's ligament, the lower limit of the block lying above the origin of the profunda artery.

In this patient, as in Case 6, peripheral vascular disease was the factor which first drew attention to the underlying mitral stenosis. We believe it likely that the extent of this patient's arterial occlusion may progress and eventually involve the lower aorta. Her history is described as it represents a stage through which the other six patients (Cases 1–6) had passed before developing complete aortic occlusion.

Incidentally, it may be pointed out that it would be quite impossible to differentiate the vascular lesions in the last patient from complete aortic occlusion on clinical grounds alone. This can be done only by means of an aortogram.

In this series four out of six patients were women. This reflects the higher incidence of mitral stenosis in women. It is in sharp contrast to the heavy male preponderance in aortic thrombosis of atheromatous origin. This sex distribution also suggests that these patients fall into a separate aetiological category.

The evidence available suggests, therefore, that emboli in peripheral vessels may sometimes result in occlusion of the abdominal aorta; once this has occurred the clinical picture differs in no way from the typical Leriche syndrome.

Summary and Conclusion

Six patients are described in whom mitral stenosis, auricular fibrillation, and aortic occlusion of gradual onset were observed. There is evidence that the Leriche syndrome may be an unusual end-result of peripheral emboli in patients with mitral stenosis.

Our thanks are due to Dr. J. Litchfield, Professor Charles Rob, and Mr. Lance Bromley for their helpful co-operation, and for referring cases for examination.

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The *Disabled Persons (Employment) Act (Northern Ireland), 1960*, includes sections on the minimum age for attendance at courses, amendments as to registration, the provision of sheltered employment by local authorities, and preference for ex-service women in selection for vocational training and industrial rehabilitation courses and for possible employment.

D

IDIOPATHIC STEATORRHOEA AND HAEMORRHAGE DUE TO MALABSORPTION OF VITAMIN K

BY

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Fanconi (1927) described a haemorrhagic diathesis in three patients with coeliac disease. Later he suggested that this might be due to vitamin-K deficiency (Fanconi, 1938). Kark *et al.* (1940) noted haemorrhages associated with idiopathic steatorrhoea; there was a prolonged prothrombin time that was shortened by administration of vitamin K. A patient with sprue, complicated by haemoptysis and haematuria, was found to have a prolonged prothrombin time (Collins and Hoffmann, 1943). Cooke *et al.* (1953) reviewed 100 cases of idiopathic steatorrhoea and reported an incidence of bleeding in 10%. Haemorrhage was found most often in the skin, but haematuria, haemarthrosis, and bleeding from the gastro-intestinal tract were sometimes present.

On occasion the malabsorption may be discovered in retrospect; Butler and Young (1955) reported a case presenting with severe subcutaneous haemorrhages and menorrhagia. The coagulation time and prothrombin time were both greatly prolonged; the patient responded rapidly to blood transfusion and intravenous vitamin K_1. Subsequent investigation revealed an idiopathic steatorrhoea.

Case Report

A man aged 43 was admitted to hospital on February 3, 1959, with a history of haematuria for five days and extensive bruises and petechiae, especially on the legs but also on the face, chest, and back. He had been treated for diarrhoea, diagnosed as amoebic dysentery, in 1942 while serving in India; after that his bowels had acted normally until 1954, when he had occasional attacks of diarrhoea. This had become worse since 1957, and investigations revealed the presence of steatorrhoea.

On admission there was evidence of an acute haemorrhagic illness, a smooth red tongue, and gaseous abdominal distension. The Hess test was positive and the one-stage prothrombin time was prolonged to 150 seconds (control 18 seconds). Blood examination showed a moderate macrocytic anaemia with leucopenia: haemoglobin, 75% (11.1 g./100 ml.); red cells, 3,020,000/c.mm.; colour index, 1.24; the red cells showed marked anisocytosis, poikilocytosis, and polychromasia; they appeared normally haemoglobinized, and many were macrocytic; white cells, 2,700/c.mm. (neutrophils 75%, lymphocytes 14%, monocytes 11%); platelets, 406,000/c.mm.; serum calcium, 8.1 mg./100 ml. A sternal marrow aspiration showed active erythropoiesis which was chiefly normoblastic but with a moderate incidence of transitional megaloblasts; granulopoiesis and platelet formation appeared normal. Stool microscopy was negative for cysts and amoebae, and cultures were negative for pathogens; the total faecal fat was 45% of the dry weight of the stool (split fat 33% and unsplit fat 12%).

Subsequent barium follow-through radiographs showed some dilatation of the ileum with increase in size of the mucosal folds—appearances consistent with an idiopathic steatorrhoea. Biopsy of mucosa of the upper jejunum showed marked flattening and atrophy of the villi—appearances very suggestive of idiopathic steatorrhoea. The diagnosis was therefore confirmed as idiopathic steatorrhoea.

The haemorrhagic condition responded rapidly to vitamin K_1, first intravenously and then intramuscularly. By the third day haematuria had ceased and there was no further bruising. 48 hours after treatment the prothrombin time was 24 seconds (control 18 seconds), and after a further seven days it was 19 seconds.

Folic acid and calciferol were given orally and he was put on a gluten-free diet with normal allowance of fat and protein. Within four weeks the anaemia had cleared up: haemoglobin, 102% (15.1 g./100 ml.); red cells, 4,930,000/c.mm.; packed cell volume, 43%; white cells, 5,300/c.mm., with a normal differential count.

When seen nearly nine months later (October 23) he had gained considerably in weight and reported a normal bowel habit, the blood picture was normal, and serum calcium was 10.3 mg./100 ml.

Discussion

It was decided that this case should be published, in spite of the absence of detailed studies of the coagulation deficiency, to draw attention to the importance of haemorrhagic manifestations in the malabsorption syndrome. Though this complication is fairly well recognized, many regard the incidence as slight. In a symposium on disorders of the small intestine at the Royal Society of Medicine the only brief reference to a bleeding tendency due to deficient vitamin-K absorpwas by Avery Jones (1959); Pullan (1959) also mentioned that the fat-soluble vitamins (A, D, E, and K) are likely to be imperfectly absorbed in the presence of steatorrhoea.

It appears that haemorrhage associated with malabsorption has received greater emphasis in America. At a symposium on the malabsorption syndrome in New York Bossak *et al.* (1957), reporting their observations on 94 patients with idiopathic sprue, noted haemorrhagic manifestations in 26.6% of cases, varying from skin petechiae to fulminating gastro-intestinal haemorrhage. In those patients in whom the prothrombin time was determined it was prolonged to more than 3 seconds above the control in 70.2%. Wang and Bossak (1957), at the same symposium, recorded haemorrhagic manifestations in idiopathic sprue in 25 cases in a review of 82 patients seen during a period of 25 years, with an average follow-up of 5.1 years. All were considered to be due to hypoprothrombinaemia. In 13 out of 14 of these patients at the time of abnormal bleeding the prothrombin time varied between 21 seconds to over 3 minutes (control 12 seconds), in all patients the prothrombin time returned to normal after treatment with vitamin K.

Douglas (1958) investigated the coagulation deficiency in vitamin-K deficiency regardless of its pathogenesis. He found a deficiency of factor II (prothrombin), factor VII, and factor IX (Christmas factor).

Hoffman and Hewlett (1959) carried out detailed coagulation studies in a patient with idiopathic steatorrhoea and severe haemorrhagic manifestations. They confirmed Douglas's findings—that is, a deficiency of prothrombin, factor VII, and Christmas factor—and also found a deficiency of Stuart (Prower) factor. After a single intravenous injection of vitamin K_1 all four factors returned to near normal in 24 hours and to normal in five days.

Summary

A case is described of an acute haemorrhagic illness which was proved to be an idiopathic steatorrhoea; there was a greatly prolonged prothrombin time, which became normal after vitamin-K_1 therapy, and the haemorrhagic condition rapidly cleared.

Some of the literature relevant to this condition is reviewed and reference is made to the specific coagulation factors which are defective.

It is considered that further emphasis should be placed on this serious complication in idiopathic steatorrhoea.

I thank Dr. E. C. Warner for access to this patient under his care at Charing Cross Hospital.

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POSSIBLE ASSOCIATION OF MALIGNANT NEOPLASM WITH IRON-DEXTRAN INJECTION

A CASE REPORT

BY

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Recent reports of the carcinogenic properties of iron-dextran in rats and mice by Richmond (1959) and Haddow and Horning (1960) have aroused interest in the possibility of similar effects in humans. The following is a report of a patient who recently was found to have a sarcoma at the site of previous iron injections.

Case Report

A 74-year-old white spinster, known to have had a hypochromic anaemia since 1955, was investigated in hospital on three occasions: in 1955, 1959, and 1960. Frequent stool examinations revealed the presence of blood, but several series of upper and lower gastro-intestinal *x*-ray films and sigmoidoscopy failed to explain the blood loss adequately. Gastric analysis was normal. On recent admissions the prothrombin time, which was prolonged, responded once to vitamin K_1 oxide, and on another occasion the response was equivocal. Otherwise coagulation factors were normal. There was neither hepatic nor splenic enlargement nor lymphadenopathy.

Treatment consisted of whole-blood transfusions and oral iron. Between October 30 and December 4, 1956, six injections of iron-dextran ("imferon"), 2 ml. (100 mg.) each,

were administered in the left deltoid region. In February, 1960, at the time of her last admission, a moderately soft, oval, non-tender lump was noted over the left deltoid, measuring 1 by 1½ in. (2.5 by 3.8 cm.). This tumour had been observed by the patient a few weeks previously. A biopsy was taken on February 6, 1960, and the tumour was completely excised on February 15.

Pathology Reports

Biopsy (February 6). Surgical tissue specimen S 60-1910. An irregular portion of reddish white tissue of firm consistency 1.1 by 1 by 0.8 cm. surmounted by a narrow ellipse of epithelium. On section it presented a fleshy, yellowish white cut surface.

Excision Biopsy (February 15). Surgical specimen S 60-2373. An ellipse of skin 2.5 by 1.2 cm. containing a well-healed biopsy incision. It surmounted an ovoid portion of firm fibro-fatty tissue measuring 2.5 by 1.2 by 3 cm. Section through this area revealed a fleshy subcutaneous tumour nodule 1.5 by 1 cm., not encapsulated, yellow-white in colour, and firm in consistency, its deepest margin very close to the deep site of resection. The overlying skin was in juxtaposition to the tumour but was movable over the tumour surface.

FIG. 1.—Soft-tissue sarcoma, deltoid area. (×150.) Perl's iron stain, haematoxylin counterstain. Blue-staining pigment appears as dark agglomerations. (See arrows.)

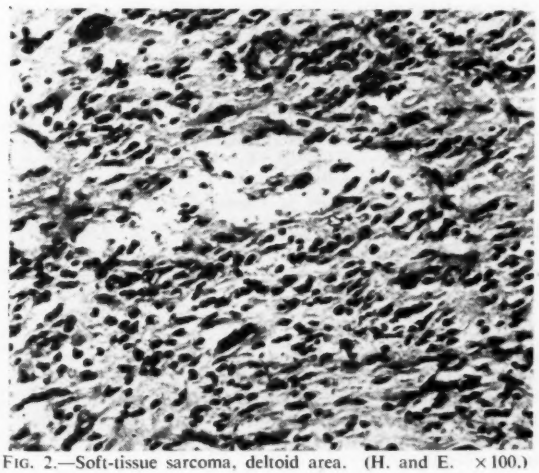

FIG. 2.—Soft-tissue sarcoma, deltoid area. (H. and E. ×100.)

Microscopically, both the biopsy S 60-1910 and the excision biopsy S 60-2373 showed the tumour to be composed predominantly of spindle-shaped cells, most of them hyperchromatic. Mitotic figures were not especially numerous. Many cells contained fat vacuoles. Mononuclear giant cell forms with abundant cytoplasm and irregular vesicular nuclei were observed, along with occasional multinucleated giant cells. The stroma was relatively scanty and of a fibro-fatty type. The tumour infiltrated the investing fibro-fatty tissue and was not encapsulated. Finely divided Prussian-blue-positive particles were scattered throughout the tumour but were most abundant in the deep peripheral areas and the superficial corium. Only in rare instances did the particles appear to occur in histiocytes. The pigment was present in both S 60-1910 and S 60-2373.

A diagnosis of "undifferentiated sarcoma, soft tissues of left upper arm" was applied.

A random 5-mm. punch biopsy of skin and subcutaneous tissue was taken from the corresponding deltoid area of the other arm and was reported (S 60-9138) as normal. Serial sections were stained by Prussian-blue method for iron and all were negative.

Discussion

Although the evidence in this case may seem to weigh in favour of an aetiological interrelationship, the possibility of a sarcoma developing coincidentally at the site of the iron-dextran injection must be considered. Sarcomas of the upper extremity and shoulder areas are by no means uncommon (Lieberman and Ackerman, 1954; Weder, 1955; Pack, 1956), and none reported has been preceded by iron injection.

We have examined sections prepared from tumours in rats produced by iron-dextran. Those examined were fibrosarcomas and differed considerably in appearance from the case under discussion. More iron appeared to be present in the animal tumours.

Slides of tissue removed from areas reputedly injected with iron-dextran up to two years previously were also reviewed (Golberg and Smith, 1960), and these demonstrated retention of iron in amounts appreciably in excess of that demonstrated in the present case.

Conclusive proof that the tumour was primary, and not a metastasis from an occult lesion elsewhere, cannot be provided at the present time.

Summary and Conclusions

A 74-year-old woman received six injections of iron-dextran (imferon) between October 30 and December 4, 1956. It is not known whether these were administered intramuscularly or subcutaneously. All were given in the deltoid area of the left arm.

A tumour mass estimated to be 2.5 by 3 cm. was first observed in February, 1960, approximately three years after her last injection of iron-dextran in the area, and was reported as an undifferentiated soft-tissue sarcoma.

Iron-dextran as a carcinogenic agent in experimental animals has been reported, and its potential as a factor in human carcinogenesis has been reviewed editorially in the *British Medical Journal* (1960) and the *Canadian Medical Association Journal* (1960).

The above case report is presented as a possible example. We make no claim that the iron pigment

identified in the tumour is injected iron-dextran and not haemosiderin. A random biopsy of skin from the deltoid area of the other arm contained no iron. The possibility that the tumour developed coincidentally at the inoculation site has been considered. It has not been proved that the tumour is primary.

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Medical Memoranda

Huntington's Chorea in Northamptonshire

The incidence of Huntington's chorea in Northamptonshire was investigated by Pleydell (1954), who found eight affected families in the county. The following year (Pleydell, 1955) a further choreic family came to light, making nine such families in Northamptonshire, with a total of 17 living affected members, and giving an incidence of 6.5 cases per 100,000 population.

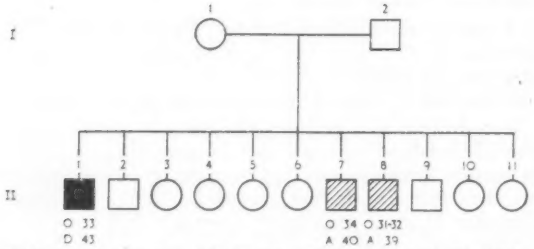
Yet another family has recently been found, and, as the affected members were in fact suffering from Huntington's chorea at the time of Pleydell's original investigation, this memorandum is presented in order to amend that author's figures. The family is also of interest because all ascertained cases of the disease occurred in the same generation.

I 1.—Free from disease. Alive, aged 81. Her mother and father both left the district, and it is thought that her mother died at the age of 45, though the cause of death could not be ascertained. Where and when her father died is likewise unknown.

I 2.—Died aged 79. Cause of death was coronary thrombosis and arteriosclerosis. No suggestion of Huntington's chorea. Both parents of this man lived till beyond the age of 80 and neither was apparently affected.

II 1.—Onset of disease at 33. Admitted to hospital and diagnosed as suffering from disseminated sclerosis. Death ascribed to cerebral haemorrhage. Hospital notes record, just before death—that is, 10 years after onset of disease—that the reflexes were not obviously exaggerated and that the Babinski plantar response was not present. Had to be nursed in a cot. True diagnosis almost certainly Huntington's chorea.

II 7.—Served in 1939–45 war. Onset of chorea at 34, and has been unemployed since shortly after that time. Now has classical signs of the disease, including gross ataxia and disturbed speech.



Pedigree of family. O=Age at onset. D=Age at death. A=Present age.

II 8.—Worked in shoe factory till onset of chorea at 31 or 32. When admitted to hospital after an accident at the age of 33, was recorded as mentally defective. Has steadily gone downhill, and at age 39 was falling about the house, required constant attention, and was suffering from advanced dementia. Speech was restricted to incomprehensible grunting sounds.

COMMENT

Although it is not shown in the accompanying pedigree, none of the three affected patients married, whereas, of their eight normal siblings, only one has remained a bachelor. The remaining seven all have families, and, while most of their children are still below the most likely age of onset, none has so far developed any signs of Huntington's chorea.

Unlike the nine families reported by Pleydell, all the cases of the disease in the present family have occurred in the same generation. The father of these patients died at the age of 79, and his family doctor states that there was no evidence of chorea at that time. The mother is still alive and remarkably healthy at the age of 81. This state of affairs is extremely uncommon. In only 6 of the 151 pedigrees quoted by Bell (1934) did the parents of one or more affected offspring live to old age without themselves developing evidence of Huntington's chorea.

Reconstructing the full family tree, only the relevant portion of which is published, was not easy. In addition to Huntington's chorea, the stigma of illegitimacy entered into the picture at various stages, and this combination made some of those who were interviewed reluctant to give information. Despite the evidence before her own eyes, the elderly mother of the affected brothers would not accept that all three were victims of the same condition. In the case of the youngest living affected member (II 8), she insisted that his condition was the result of a fall from his bicycle. Reluctance on the part of a parent to admit to the presence of a disease which affects several members of her family is perhaps understandable, as admission would no doubt be accompanied by unjustified feelings of guilt.

In conclusion, it would appear that at the time of Pleydell's investigation there were at least ten choreic families in Northamptonshire. By tracing their pedigrees a total of 72 cases were found, and at the time in question 19 patients were alive in the county, giving an incidence of 7.2 cases per 100,000 population.

I am grateful to Dr. C. M. Smith, Dr. G. O'Gorman, and Dr. M. J. Pleydell for their advice and help, and to the staff of the mental health section of the County Health Department for their assistance in establishing the pedigree.

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The Morison Medals, which are awarded by the Royal College of Physicians of Edinburgh to members of the nursing staffs of mental hospitals in Scotland in recognition of long and meritorious service, were presented at a recent College meeting to Miss Margaret D. Morrison (matron-superintendent, Broadfield Institution, Port Glasgow, Renfrewshire) and Mr. Andrew S. Wisley (chief male nurse, Murray Royal, Perth).

Reviews

UNDULANT FEVER

Brucella Infection and Undulant Fever in Man. Sir Weldon Dalrymple-Champneys, Bt., C.B., D.M., D.P.H., F.R.C.P. (Pp. 196+xii; illustrated. 25s.) London, New York, Toronto: Oxford University Press. 1960.

The author of this book has made a special study of undulant fever (a term which he prefers to "brucellosis") since 1928, when he was largely responsible for its recognition as an indigenous disease in this country. The clinical chapters are based on 1,500 cases of which he has records, and his extensive material serves admirably for a detailed analysis of every feature of the disease. This is preceded by a historical account—illustrated by photographs drawn from Bruce, Zammit, Alice Evans, and others—and a description of the infection in animals, and followed by chapters on diagnosis, prevention, and treatment.

There are few bacterial infections of which the diagnosis can be so difficult as undulant fever, and this full and authoritative account will afford welcome guidance both in clinical assessment and in the interpretation of diagnostic tests. Specialists in this infection are apt to see it in almost any patient suffering from obscure chronic ill-health, and to rely on diagnostic proceedings the specificity of which is doubtful. The author admits that chronic brucellosis may exist without abnormal physical signs, and that agglutinin may be absent from the blood even in cases proved by positive cultures, but he denies the significance of the opsono-cytophagic reaction and of agglutinin provoked by brucellin. The chapter on treatment has a good deal to say about immunization and desensitization, two proceedings sharply distinguished here in their theory of action, although it must surely sometimes be a little difficult to know which is being achieved. This follows a detailed analysis of the merits of different systems of antibiotic treatment, which with its emphasis on toxic effects and on an invariable residuum of failed cases is perhaps necessarily a little discouraging.

This is not the first book on this subject to appear in the English language, but it is the first to be published in this country. The wealth of information it contains, and particularly its sanity of outlook, should make it welcome on both sides of the Atlantic.

L. P. GARROD.

PRIMATES' TEETH AND JAWS

The Jaws and Teeth of Primates, Photographs and Commentaries. By W. Warwick James, O.B.E., F.R.C.S., M.Ch., F.D.S., F.L.S. (Pp. 328+xii. £5 5s.) London: Pitman Medical Publishing Co., Ltd. 1960.

This is a remarkable work by a remarkable man. The author is to be congratulated on his enterprise and the energy with which he has carried out his design. Fundamentally the book is a photographic atlas of the dentition and gnathic morphology of the whole series of Primates from the Tupaioidea to the Pongidae.

The photographs, which are excellent from the technical point of view, are taken mainly from skulls in the collection of the British Museum (Natural History) and include, therefore, examples of even the least-known genera—e.g., *Arctocelus, Callimico, Brachyteles, Rhinopithecus.* Each representative is depicted in three aspects, all taken more or less from oblique angles with the object of revealing as much detail as possible of the dental morphology. The first shows the two jaws in oblique lateral view, the second a palatal view of the upper dentition, and the third an oblique view from above of the mandibular series. In a few instances additional studies are given of the deciduous dentition or of the permanent series after removal of the outer alveolar bone to reveal the dental roots. The collection is therefore unique. Each group of photographs (i.e., every genus, and in some cases several species in a genus) is supplied with a brief summary of the dental features depicted. Interpolated are descriptive notes dealing with the classification of the major groupings, and biological data. The latter include indications of the diet with an attempt to correlate dental and gnathic morphology with functional demands.

There are also useful introductory chapters dealing with some general problems, taxonomic, nomenclatural, temporo-mandibular joint morphology, and some aspects of odontogenesis. Unfortunately from the student's point of view no consideration is given to the important question of the terminology of molar cusps or their homologies in the different groups; nevertheless, reference is made to well-known earlier works—e.g., Cope, Osborn, Gregory, and Forster Cooper, in which such matters are discussed. The work concludes with appendices which supply additional information on development, on the temporo-mandibular joint, and notes (by L. G. Smith, of the London Zoo) on animal husbandry as applied to Primates.

This work will long remain a useful reference volume for the specialist, but will supply a long-felt want for teachers and students. A few words of criticism are, however, needed. Nomenclature is not everywhere up to date, and there are some inconsistencies (e.g., Lemuroidea is used on p. 44, and Lemuriformes for the same group on p. 77). A serious lapse in proof correction occurs on p. 143 when *Logothrix* stands for *Lagothrix*—correctly used elsewhere—and there are several more in the bibliography. Two species of *Colobus* are considered, both, however, pertaining to the black and white section of the genus; why, then, omit the red and olive *Colobi*? On the other hand, it is welcome to find the author dispelling the old illusion respecting the molar tubercles in *Miopithecus* (p. 209).

W. C. OSMAN HILL.

EIREAN HEALTH SERVICES

The Health Services of Ireland. By Brendan Hensey. B.Comm., Dip.Pub.Adm. (N.U.I.). (Pp. 168. 15s.) Dublin: Institute of Public Administration. 1959.

This book sets out in clear terms the development, functions, organization, and finance of the health services of the Republic of Ireland. Until the separation, now nearly 30 years ago, the pattern with minor differences followed that of England and Wales, and any major act of Parliament for the latter was soon followed by one, with suitable variations, applying to Ireland. Now the differences between the two countries are more marked. There is in Ireland no National Health Service providing free treatment for all, and the general structure is not unlike that of England and Wales before 1948.

A free general medical service is provided only for the lowest income group numbering about 30% of the population. It is carried out by district medical officers, the former "dispensary medical officers." The hospitals contain 56,829 beds and have not been nationalized. About 55% of the population are in the middle-income

group and are entitled to in-patient treatment free or at a reduced charge. For the 15% in the higher income group, which appears to comprise those with an annual income exceeding £800, there is a State-sponsored voluntary insurance scheme to help them to pay for hospital care. By December, 1958, 57,000 policies had been taken out.

Most of the Dublin hospitals are voluntary: in the rest of the country they are generally administered by the cities and the counties. The country contains many fine new hospitals largely built by money from the Irish Hospitals' Sweepstakes. Those who contributed through this channel may like to know the result: up to October, 1958, £44.5m. had been allocated to the Hospital Trust Fund; £11m. of it went on stamp duty; £10.5m. were spent on paying deficits on the running costs of voluntary hospitals, leaving £23m. available for capital expenditure. Since April, 1948, £17m. have been actually spent, and to this sum were added £6.8m. by Exchequer subvention and about £3.6m. by local authorities, making a total capital expenditure on hospitals of £27.4m.—a figure which for a small country puts some of the larger ones to shame.

The system of local government is interesting in that each city or county has a manager to whom is delegated important functions which in this country are reserved for the elected members. The differences and similarities between this country and Eire are of great interest to the student of government and are worthy of study: they are more marked in the provision of curative than of preventive medical services. The book is authoritative, but not too big, and is easily read. There is a good index.

ALLEN DALEY.

CASTRATION

Asexualization. A Follow-up Study of 244 Cases. By Johan Bremer. (Pp. 366. 35s.) New York and London: The Macmillan Company. 1959.

Apart from some minor shortcomings, this book is one of the best psychological studies of the effects of castration that has been published recently, and it should not be omitted from any reference library.

The author reports and evaluates the results of castration in 216 men, 102 of whom were sex offenders and the remainder psychiatric cases, mainly schizophrenics, mental defectives, or epileptics showing pathological sexual behaviour. The case material is very well presented in numerous tables, and there are many very interesting individual case histories. The author's conclusion is that, of all the patients investigated, only 22 sex offenders would have relapsed if they had not been castrated.

The book also contains a chapter dealing with the castration of women. The therapeutic results, however, are negligible, and the author comes to the conclusion that there is definite doubt as to its justification. The therapeutic effect of castration carried out for psychiatric reasons before the climacteric age is so slight that this indication for its use can be disregarded.

The title of the book is misleading. Castration cannot be said to be equivalent to "asexualization"; sexuality, particularly in the adult human being, depends not only on the gonads but on a great many other factors which it would not be possible to enumerate in the frame of a review.

In the introduction, the author attempts a survey of previous studies on castration as carried out in various countries. This survey is very incomplete, and one might wish that more emphasis had been placed on the psychological and physiological sequels of castration in those areas in which it has been carried out for thousands of years for religious reasons, or, as in Nazi Germany, where the operation has been performed for political ends.

It is regrettable that the endocrine changes found in these patients by clinical or laboratory investigations were not co-ordinated with the psychological changes. It might also be mentioned that to suppress pathological sexual compulsions in men castration is no longer the method of choice: treatment with oestrone or stilboestrol should suppress the sex drive much sooner than surgical castration.

MAX REISS.

WELL-BOUND SHADOWS

The Mediastinum. By Ted F. Leigh, M.D., and H. Stephen Weens, M.D. (Pp. 246+x; illustrated. 92s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

This monograph, compiled by two professors of radiology at Emory University, is 240 pages in length. It has an index, 290 radiographs, and anatomical drawings, and is concerned with explaining the various mediastinal shadows that occur in radiographs.

The general arrangement of the book is this. There are 30 short chapters each one of which gives a brief factual description of a topic—such as teratomas. This includes the aetiology, the pathological anatomy, methods of investigation, and a list of recent references for more detailed study. Throughout the text of these chapters a number of typical radiographs are reproduced, and the captions of these describe the salient diagnostic radiological features. Special attention has been paid to the radiology of the normal mediastinum, to lesions of the lymph nodes, to neurogenic lesions; and to the oesophagus, the diaphragm, and the adjacent chest wall. Rare conditions are also depicted.

The book is well bound; it is printed on good paper and the quality of the radiological reproductions is adequate. It will be a valuable addition to the reference libraries of radiologists and all who are concerned with the diagnosis and treatment of chest diseases.

N. R. BARRETT.

JEWISH MEDICAL ETHICS

Jewish Medical Ethics. A Comparative and Historical Study of the Jewish Religious Attitude to Medicine and its Practice. By Rabbi Dr. Immanuel Jakobovits. (Pp. 381+xlii. 42s.) New York: Philosophical Library. London: H. Pordes. 1959.

Biblical and Talmudical medicine are of interest in that they represent and document fully that important and long phase of medical history when medicine and theology were closely related. For part of that time the physician and priest were one and the same person, for the rest medical practice carried heavy theological overtones. This highly specialized monograph by Rabbi I. Jakobovits covers very much the same ground as the classical studies by Preuss in German and by Katzenelsohn in Hebrew. It is, however, narrower in its scope and seeks to establish a consistent ethical pattern throughout the centuries of Biblical medicine.

It may be questioned whether such an attempt is feasible, for Biblical medicine not only persisted but also evolved over centuries, and ethical points of view of necessity changed throughout that evolution. The

frequent references in this thesis to conflicting opinions on relatively simple issues are in themselves evidence of the lack of any consistent ethical philosophy. At the very most there was some ill-defined general trend, and it is gratifying to know that much of Biblical medicine was rational. Dr. Jakobovits goes, however, rather far in his thesis when he suggests that Biblical medicine, as he reconstructs it, has a valid message to-day. The conditions under which medical practice in Biblical times developed, grew, and became modified do not seem to have much relevance to present-day problems. These are perplexing enough as it is, and to try to revive ethical concepts of an earlier age is no more helpful than to try to revive the conditions in which they flourished. As a contribution to medical folklore this book has its place, for it is scholarly on its factual data.

ARNOLD SORSBY.

AMERICAN PREVENTIVE MEDICINE

Preventive Medicine. Principles of Prevention in the Occurrence and Progression of Disease. Edited by Herman E. Hilleboe, M.D., and Granville W. Larimore, M.D. (Pp. 731 + xxi; illustrated. 84s.) Philadelphia and London: W. B. Saunders Company. 1959.

This book is written for medical students, general practitioners, specialists, and professional workers in official and voluntary health agencies. It contains 41 chapters and an introduction. It is arranged in three parts; prevention of occurrence, prevention of progression, and supporting services for preventive medicine.

The first part of the book sets out the principles which govern the work of public health in environmental hygiene, the protection against infections and parasites, the provision of proper and adequate nutrition, the elimination of disease conditions (obesity, the maternity cycle and the newborn period, and preventive health services in childhood). The second part deals with screening techniques, rehabilitation, alcoholism, and narcotic addiction. The third part deals with education, social work, public health nursing, the role of the hospital in preventive medicine, epidemiological methods, and health agencies.

There are 31 eminent contributors. The individual chapters are for the most part of a high standard, but, as must be expected in a book by many authors, there is a lack of sequence in the thought and argument. Some chapters go rather more deeply into clinical medicine than appears to be necessary in a public health textbook, while in others, as, for example, that on venereal diseases, the public health aspects are almost entirely ignored. The legal background to constructive public-health work is insufficiently presented.

For readers outside the North American continent the greatest weakness of the book is its failure to examine the problems of the organization of medicine, the significance of social security, and the machinery and philosophy of public health.

The book has been written by Americans essentially for Americans; nevertheless it can be recommended to students of public health in any country.

FRASER BROCKINGTON.

Under the slightly modified title of *World Directory of Venereal-Disease Treatment Centres at Ports*, the World Health Organization has published a new edition of the list of centres in ports throughout the world at which merchant seamen can obtain treatment for venereal disease. (W.H.O Palais des Nations, Geneva. 1959. 162 pp., 8s. 6d., bilingual publication—English and French.)

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Intestinal Tract: Structure, Function and Pathology in Terms of the Basic Sciences. By Richard Paul Spencer, A.B., M.A., M.D. (Pp. 411+xvii. £5 2s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Practical Proctology. By Louis A. Buie, Sr., M.D., F.A.C.S. Second edition. (Pp. 737+xvi; illustrated. £9.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

A Textbook of Gynecology. By Laman A. Gray, M.D., F.A.C.S., F.A.C.O.G. (Pp. 470+xv; illustrated. £6 4s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Fellowship of Surgeons. A History of the American College of Surgeons. By Loyal Davis, M.D., F.A.C.S. (Pp. 523+vi. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Histoplasmosis. Edited by Henry C. Sweany, M.D. (Pp. 538 +xiv; illustrated. £5 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Enzymes in Health and Disease. Edited by David M. Greenberg, Ph.D., and Harold A. Harper, Ph.D. With 26 contributors. (Pp. 459+xvi; illustrated. £5 16s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Clinical Medicine and the Psychotic Patient. By Otto F. Ehrentheil, M.D., and Walter E. Marchand, M.D. With the collaboration of other members of the staff of the Veterans Administration Hospital, Bedford, Massachusetts. (Pp. 383+xxii; illustrated. 86s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Infant Foods and Feeding Practice. A Rapid Reference Text of Practical Infant Feeding for Physicians and Nutritionists. By Herman Frederic Meyer, A.B., M.D. (F.A.C.P., F.A.A.P.). (Pp. 332+xxviii; illustrated. 78s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

Neoplastic Disease at Various Sites. General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R. Introductory Volume: ***A Clinical Prospect of the Cancer Problem.*** By D. W. Smithers, M.D., F.R.C.P., F.F.R. (Pp. 232+xv; illustrated. 37s. 6d.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

Die Hals- Nasen- Ohren- Krankheiten im Kindesalter. By Dr. P. Biesalski. With a chapter on *Die Störungen der Stimme und Sprache*, by Professor Dr. R. Luchsinger. (Pp. 342+xii; illustrated. DM. 49.) Stuttgart: Georg Thieme Verlag. 1960.

Medicinal Plants of the Arid Zones. Arid Zone Research XIII. (Pp. 96. 15s.) Paris: UNESCO. London: H.M. Stationery Office. 1960.

Viral Infections of Infancy and Childhood. A Symposium of the Section on Microbiology, the New York Academy of Medicine. Edited by Harry M. Rose, M.D. (Pp. 244+xi; illustrated. $8.) New York: Hoeber-Harper. 1960.

Clinical Physiology. Volume I: ***Electrolyte Balance, Water Metabolism, Renal Function, Gastro-Intestinal Function, Hepatic Failure.*** By Kathleen E. Roberts, M.D. (Pp. 226+xi; illustrated. $6.50.) San Francisco: Filmer Publishing Co. 1960.

Die Zellkernmorphologische Geschlechtserkennung in Theory und Praxis. By Dr. Hermann Adolf Heinz. (Pp. 219+x; illustrated.) Heidelberg: Dr. Alfred Hüthig Verlag GMBH. 1960.

Grundriss der Gesamten Chirurgie. By Fritz Holle, with the assistance of H. P. Jensen. Seventh, revised, edition of *Grundriss der Gesamten Chirurgie*, by E. Sonntag. In two volumes. (Pp. Vol. I: 920; Vol. II: 921–1,957; illustrated. DM. 88.) Berlin, Gottingen, Heidelberg: Springer-Verlag. 1960.

Electrophysiology of the Heart. By Brian F. Hoffman, M.D., and Paul F. Cranefield, Ph.D. (Pp. 323+xi; illustrated. 97s.) New York, Toronto, London: The Blakiston Division, McGraw-Hill Publishing Company, Ltd. 1960.

Atrial Septal Defect. An Investigation into the Natural History of a Congenital Heart Disease. By H. Gösta Davidsen. (Pp. 225; illustrated. Dan. kr. 50.) Copenhagen: Munksgaard. 1960.

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TOWARDS ACCEPTANCE

The Joint Working Parties, composed of representatives of the profession and of officials of the Ministry of Health, have completed their tasks—the one for consultants and hospital staff and the other for general practitioners. The report of the Central Consultants and Specialists Committee on this was presented last week to the B.M.A. Council by Dr. T. Rowland Hill (deputizing for Mr. H. H. Langston), and Dr. A. B. Davies gave the report of the General Medical Services Committee, of which he is the chairman. These two reports, and the Council's debate on them, are published in this week's *Supplement*, together with the Council's own report on the matter which will go to the Special Representative Meeting on September 28. To fit in the other pieces of this democratic jigsaw puzzle, the G.M.S. Committee's report will be considered by a special Conference of Representatives of Local Medical Committees on September 27, and the C.C. and S. Committee's report by the Regional Consultants and Specialists Committees, whose observations will be considered by the C.C. and S. Committee on September 8. Then on September 13 the views on the Working Party's report of *its* constituent bodies will be examined by the Joint Consultants Committee. Nor must we omit from all this the Branches and Divisions of the B.M.A.

The terms of reference for the S.R.M. of September 28 are as follows:

> "To consider, in the light of the reports of the Joint Working Parties on the detailed application of the Report of the Royal Commission on Doctors' and Dentists' Remuneration, the Minister's offer to implement the Royal Commission's recommendations as a whole and as they stand."

The Council's recommendation to the S.R.M. is as follows: "That the reports of the Joint Working Parties, and the Ministers' offer to implement the recommendations of the Royal Commission as a whole and as they stand, be accepted." In making the "package deal" with the Government the profession accepted a collective obligation for a settlement of the pay-claims of both general practitioners and of hospital and consultant staff working in the National Health Service. That is to say, if the recommendations of the Joint Working Party on General Practitioner Remuneration were not accepted by the Conference of Local Medical Committees, then hospital staff and consultants would not receive any extra pay even though *their* Joint Working Party report commended itself to their representative organizations, and vice versa. Whatever the merits and justice of the case of either of these two main professional groups in the N.H.S., the Government has insisted on "the all-or-none principle." And the profession has agreed to this. The profession's representatives in the two Working Parties were therefore faced with a dilemma.

As the report of the Council's debate in this week's *Supplement* shows, the G.P. Working Party at one point reached an impasse from which it emerged only by agreeing to postponing the settlement of £1m.: this was *not* in the Royal Commission's recommendations "as a whole." The distribution of this £1m. is to be settled by a further Working Party. And if the profession's representatives had not agreed to this then the rest of the pay settlement—both for general practitioners and for hospital staff—would have been suspended. As the profession, the Press, and the people through Parliament have accepted the pay recommendations of the Royal Commission as by and large reasonable for a body of professional men and women who have for some years been paid less than they should have been, this procedure must strike any detached observer as dealing out justice in a very rough way. But given the unusual conditions of the "package deal" the profession's representatives in the G.P. Working Party had perforce to agree, if only for the reason that disagreement to a point of deadlock would have jeopardized the position of their colleagues—especially their junior colleagues—in the hospital service.

These are the hard and stubborn facts of the case, and no amount of wishful talking can explain them away. The profession would seem to be more firmly under the control of the Government than ever before. A member of the C.C. and S. Committee said at the Council last week that his Committee accepted the Working Party proposals but wanted it made clear that acceptance did not mean approval. This will probably be the verdict of the various professional groups that meet and report between now and the S.R.M. on September 28. The collective obligation incurred by both hospital staff and general practitioners makes it unlikely, and, we believe, undesirable, that either will do anything to jeopardize the speedy

settlement of the pay claim of the other. Though predictions may be falsified, it therefore seems safe to forecast that by the end of September the profession as a whole will accept the reports of the two Joint Working Parties.

The facts and figures of the reports are set out in this week's *Supplement*. The main controversial item in the Council debate was recommendation XV of the Joint Working Party on General Practitioners' Remuneration, which is as follows: "A sum of £1m. per annum should be reserved from the distribution of available money so that further consideration can be given to methods of making the best possible general medical service available to the public. A further Working Party of representatives of the profession and the Health Departments should be appointed to consider this matter." That many members of Council were uneasy about this as a matter of principle is clear from the debate (see *Supplement*, p. 89). What was also clear was that Dr. A. B. Davies had been faced with an appallingly difficult problem and had, with his professional colleagues on the Working Party, found a solution that had made it possible for them to avoid a complete breakdown of negotiations. It is deeply to be regretted that the Ministry side sought to impose on general-practitioner representatives something not in the recommendations of the Royal Commission. Dr. Davies's colleagues in general practice owe him a deep debt of gratitude for the enormous amount of work he has put in on their behalf and for his courage in taking a course that he knew would be open to criticism. And everyone will sympathize with his remark that "perhaps no one in the profession had had to bite his lips more than he had over the so-called 'package deal.'" In the search for clarification of item XV, no one at last week's Council meeting seems to have noticed item iii (b). This begins by saying that there should be no immediate reduction in the size of lists, and goes on: "The question of the future size of lists should be considered by the Working Party mentioned at paragraph XV below." It seems to be worth while drawing attention to this.

Dr. T. Rowland Hill, in his report to the Council, drew attention to certain "blemishes" in the Working Party Report made by the Departments of Health and the Joint Consultants Committee. Among them were the following:

(1) The new consultant joining the service takes ten years to reach his maximum salary. (2) The abolition of weighting meant lack of continuity of responsibility —involving a financial loss and the sacrifice of a principle. (3) The loss of some of the travelling allowances for part-timers. (4) The difficulty of administration involved in the payment of retrospective money to locums. (5) The remuneration of senior registrars of nine and subsequent years' standing—and, indeed, the whole future prospects of senior registrar jobs.

These and other matters the C.C. and S. Committee wishes to raise in future with the Review Body or with Committee B of the Medical Whitley Council. Dr. Hill said that his Committee would waste no time in preparing a report with this end in view. Mr. Enoch Powell, the new Minister of Health, on August 12 sent to the Association a letter on the Review Body (see *Supplement*, p. 71) in which he states that copies of any submissions made to this body by the Government would also be made available to the profession, and vice versa: "In fact, we agreed during our talk that the Ministry of Health would act as a post-box for representations of this kind to the Review Body, and that the correspondence should be open to all parties concerned." After the publication of the Royal Commission Report the B.M.A.'s spokesmen stressed that the profession must have direct access to the Review Body as of right. Mr. Powell's letter does not carry us any further in this respect, noting only that the Review Body "might wish to receive further representations or information direct from either party . . . and it would be for the body itself to decide how far this further evidence would be made known, at once or later, to the other party. . . ." When the Review Body is set up, we hope that it will speedily put the mind of the profession at rest by granting it something to which it attaches the highest importance—the right of direct access.

MODERN TREATMENT OF LEPROSY

The leprosy hospital or settlement used to be a kind of medical slum. Though the unfortunate patients evoked pity, their case was so hopeless that little could be done except nurse them until they died, and even that took painfully long. But the last 20 years have seen great advances. Leprosy has changed from being a hopeless horror to being a relationship between host and invading pathogen that can be successfully challenged, and there is the cheerful conviction that most patients with leprosy can eventually be cured, though it may still take a long time. The fundamental advance during this period has been the introduction of dapsone (diaminodiphenyl sulphone) by J. Lowe[1] and others. This has now become the standard treatment, given in doses

approximating to 300 mg. twice weekly. It has the advantages that it cures most patients in the long run, it never produces resistant bacilli, it seldom produces dangerous complications if given with reasonable care, and it is cheap. Since great numbers of patients must be treated for long periods in poverty-stricken countries, this last attribute is important. All the same, dapsone is not the perfect drug for leprosy, and there have been many attempts to produce drugs which act more rapidly or which are less apt to produce untoward effects or lepra reactions.

In the first place there have been attempts to modify or mask the sulphone molecule by substituting one or both of the terminal amino groups, or by using diaminodiphenyl sulphoxide (which has one less oxygen atom than dapsone).[2] Some of these compounds may have slight advantages over dapsone, but they are not so great as to supplant the parent compound. A more hopeful compound is Ciba 1906 (D.P.T., 4-butoxy-4-dimethyl-amino-diphenol-thiourea). This was first tried by T. F. Davey and G. Currie five years ago and considerable experience has now been gained with it.[3] Briefly, it is given orally as 2 g. daily for an adult. It is slightly more active than dapsone, as judged by the disappearance of bacilli in lepromatous cases. In two to three years signs of drug resistance may appear, so it should not be continued after that period. Its chief advantage is that it is less toxic than dapsone; in particular, it is less harmful to the liver and it has less tendency to provoke lepra reactions or erythema nodosum. Accordingly it is the drug of choice for debilitated patients or for those on dapsone who have complications such as psychosis, neuritis, or the reactions already mentioned. It is rather expensive, especially when the much bigger dosage is taken into account; on the other hand, if it allows treatment as an out-patient instead of an in-patient it may be an economy in the long run.[4] There is some evidence that its therapeutic effect depends on its conversion to a more active metabolite.

The next drug was "etisul" (diethyldithiol *iso*-phthalate), which is somewhat unconventional. Compounds of this type (ethylmercaptans) had long been known to be active against acid-fast bacilli, but their clinical application was hindered by their stench. However, acceptable preparations have been provided by the addition of suitable perfumes, and etisul can now be given twice weekly by inunction over a large area of the body. When given to lepromatous patients in this way Davey[3] found that there was often a remarkable reduction in the number of biopsy specimens of skin, a change in their morphology, and a distinct clinical improvement in the patient. These effects are greater than can be produced by other drugs and they have been confirmed elsewhere. After three to six months signs of drug resistance may appear, and the patients tend to become weary of the treatment. Accordingly this compound is best given in conjunction with dapsone or Ciba 1906, and after three months the etisul is discontinued.

Many other drugs have been tried,[2] but none have been outstandingly successful. Cortisone and related steroids have been found valuable in controlling lepra reactions provoked by dapsone; and unless their administration is unduly prolonged they do not seem to do harm by weakening the body's defences against this infection.

Changes in the morphology of bacilli during treatment with etisul or even with dapsone can be seen in the ordinary Ziehl–Neelsen smear, but they are better studied by the electron microscope.[5 6] When the disease is active and progressing, many of the bacilli are normal in shape and presumably alive, but even at this stage many appear degenerate and are presumably dead. When the disease is regressing, either spontaneously or under treatment, most of the bacilli are certainly defunct. They are corpses of bacilli which the body finds difficult to digest and remove. In Ziehl–Neelsen smears they appear granular and stain poorly; they can be ignored as evidence of active disease. Reactivation of the disease (if it should take place) is preceded by the reappearance of bacilli with normal shape and staining reactions.

Among other aspects of leprosy on which research is proceeding, the nature of the lepromin reaction has been critically reconsidered. It had always been assumed that a positive lepromin reaction was analogous to a positive tuberculin reaction, and that it indicated hypersensitivity of the body induced by the infection specifically to certain chemical fractions of the leprosy bacillus. But now evidence is accumulating[7] that the lepromin reaction may depend

[1] Lowe, J., *Lancet*, 1950, **1**, 145.
[2] Bushby, S. R. M., *Pharmacol. Rev.*, 1958, **10**, 1.
[3] Davey, T. F., *Trans. Roy. Soc. trop. Med. Hyg.*, 1960, **54**, 199.
[4] Garrod, J. M. B., *Leprosy Rev.*, 1959, **30**, 210.
[5] McFadzean, J. A., and Valentine, R. C., ibid., 1960, **31**, 6.
[6] Rees, R. J. W., Valentine, R. C., and Wong, P. C., *J. gen. Microbiol.*, 1960 **22**, 443.
[7] Kooij, R., and Gerritsen, Th., *Int. J. Leprosy*, 1956, **24**, 171.
[8] Wallace, J. H., Elek, S. D., and Hanks, J. H., *Proc. Soc. exp. Biol. (N.Y.)*, 1958, **97**, 101.
[9] Rees, R. J. W., and Wong, P. C., *Nature (Lond.)*, 1958, **181**, 359.
[10] Chatterjee, K. R., *Int. J. Leprosy*, 1958, **26**, 195.
[11] Binford, C. H., ibid., 1958, **26**, 318.
[12] Gunders, A. E., *J. trop. Med. Hyg.*, 1958, **61**, 228.

only on raised sensitivity to almost any foreign substance introduced into the skin. Secondly, great efforts are being made to induce leprosy bacilli to multiply either in laboratory animals or in tissue cultures. Limited multiplication—namely, two to four generations—of the rat leprosy bacillus has been obtained in tissue cultures by J. H. Wallace and colleagues[8] and R. J. W. Rees and P. C. Wong.[9] Material from lepromatous patients has also been inoculated into animals and growth of acid-fast bacilli has been obtained in black mice,[10] in hamsters,[11] and in chimpanzees.[12] The past history of leprosy is strewn with so many premature claims that all reports must be regarded with scepticism until it is proved beyond all doubt whether the bacillus which has been isolated is really Hansen's bacillus or only some previously unrecognized mycobacterium, of which unfortunately there are many. Nevertheless, leprosy has now changed from a subject of despair to one of active, and optimistic, research.

MINOR RESPIRATORY INFECTIONS IN CHILDHOOD

Several recent surveys have been concerned with the prevalence and mode of spread of minor respiratory infections in childhood. The highest attack rate appears to be in the age group 2 to 4,[1] but this is greatly influenced by the extent to which these children mix with children going to school; it is likely to be at the age of 5 to 6 in "only" children.[2] O. M. Lidwell and T Sommerville,[3] working in Wiltshire villages, concluded that the presence of schoolchildren in a household doubled the number of colds experienced by infants under the age of 5. F. S. W. Brimblecombe and colleagues,[4] studying families in Paddington, were equally impressed by classrooms as sources of infection. They considered many possible social and environmental factors in addition, and decided that, once an infection had been brought into a home, its spread within the family depended principally on the degree of overcrowding and, to a less extent, on the adequacy of clothing. Indeed, the propagation of colds and other minor respiratory infections appears to be much more closely related to noisy classrooms and overcrowded homes than to any widespread dissemination of droplet spray.[5] The average number of fresh respiratory infections in schoolchildren has been estimated at five or six each year.[1 4] In seeking an explanation for this massive invasion, we are immediately faced with the enigma of the common cold. Moreover, dozens of new viruses have been isolated from the air passages in the past ten years, many of which have been shown to cause respiratory symptoms. As yet, laboratory tests for specific strains are usually negative in individual attacks, which suggests that more remain to be identified. Undoubtedly these recurring infections derive mainly from the welter of potentially pathogenic viruses to which children are exposed.

The relative importance of natural as opposed to acquired immunity which determines the fall in prevalence after the age of about 7 years remains to be determined. The mechanism of individual susceptibility of "catarrhal children" has been considered by R. Grenville-Mathers,[2] who reviewed 675 children referred to the Harrow Chest Clinic. He found a big increase in respiratory infections when they started to go to school, which persisted until the age of 7, to be followed by a decline in all groups except asthmatics, in whom the frequency tended to persist unchanged throughout childhood. Perhaps more emphasis should be placed on the importance of possible allergic aspects, which clearly influence the pattern and duration of respiratory infections, if for no other reason than to assess the prognosis more accurately.

Attempts to reduce the number of respiratory infections by artificial means have been singularly unsuccessful. They have included ultra-violet irradiation in classrooms,[6] hexylresorcinol in offices,[7] and ultra-violet lamps, oiled floors, and screens between beds in barracks.[8] In the present state of knowledge the most effective means seem to be the sensible management of individual infections and the avoidance of overcrowding at home and in school.

PHOSPHATASES IN LEUCOCYTES

A crude subdivision of phosphatases—the enzymes which liberate orthophosphoric acid from many monophosphate-esters—is made on the basis of their optimal activity at varying *p*H. The "alkaline" phosphatases are most active at alkaline *p*H; the opposite applies to the acid phosphatases. The two groups of enzymes differ not only in their *p*H optima but also in their reactions to activators and inhibitors. Thus fluoride inhibits the acid phosphatases but is relatively ineffective with the alkaline enzyme. On the other hand, magnesium ions, which activate the alkaline enzyme, have virtually no effect on the acid enzyme. There are also important differences within the two groups—for instance, between the acid phosphatases from the red cell and from the prostate.

The leucocyte phosphatases—in particular the alkaline enzyme—have been widely studied. Cytochemically there have been two principal techniques. One associated with the names of G. Gomori[1] and H.

[1] Badger, G. F., Dingle, J. H., Feller, A. E., Hodges, R. G., Jordan, W. S., and Rammelkamp, C. H., *Amer. J. Hyg.*, 1953, **58**, 31.
[2] Grenville-Mathers, R., *Brit. J. dis. Chest*, 1960, **54**, 72.
[3] Lidwell, O. M., and Sommerville, T., *J. Hyg. (Lond.)*, 1951, **49**, 365.
[4] Brimblecombe, F. S. W., Cruickshank, R., Masters, P. L., Reid, D. D., and Stewart, G. T., *Brit. med. J.*, 1958, **1**, 119.
[5] Reid, D. D., *Lancet*, 1958, **1**, 1237.
[6] Spec. Rep. Ser. med. Res. Coun. (Lond.), 1954, No. 283.
[7] Lidwell, O. M., and Williams, R. E. O., *Brit. med. J.*, 1954, **2**, 959.
[8] Macdonald, T. C., Tonkinson, J. D., Porterfield, J., and Dumbell, K. R., *Brit. J. prev. soc. Med.*, 1955, **9**, 33.

Takamatsu[2] is based on the formation of an insoluble calcium phosphate from the hydrolysis of glycerophosphate. The calcium phosphate precipitated at the site of phosphatase activity is converted into cobalt phosphate, and this is followed by conversion to the black cobalt sulphide. This technique suffers from the disadvantage that the nuclei are often stained, whereas it is known that phosphatase is situated in the cytoplasm. A more accurate technique makes use of naphthyl phosphate. The liberated naphthol is rapidly coupled with diazotized amine to form an insoluble coloured precipitate. This method of localizing alkaline phosphatase in cells was introduced by M. L. Menten and colleagues.[3]

Many modifications of the original techniques have been proposed, of which a particularly accurate version has been published by F. G. J. Hayhoe and D. Quaglino.[4] Their diazonium salt, Fast Garnet, from *o*-amino-azotoluene, gave most rapid and satisfactory coupling when used in conjunction with α-naphthyl phosphate and propanediol buffer in a substrate to which blood and bone-marrow smears were exposed. Previous results for alkaline phosphatase of leucocytes were confirmed and expanded. Leucocytes were graded into five groups according to their staining by this technique. There were negative or colourless cells, cells with only occasional granules, cells with moderate granule formation, leucocytes which were strongly positive and showed many granules, and lastly, those with very numerous coarse granules giving an intense dark precipitate. The scoring technique described by L. S. Kaplow[5] was followed and 100 cells were examined with each individual score being recorded 0–4. The sum of 100 individual cell ratings provided the score for each specimen, with a possible range of 0–400.

A most important differentiation made by these methods is between chronic granulocytic leukaemia and high leucocyte count for other reasons. In chronic myeloid leukaemia the scores were always low, whereas in infectious leucocytosis they were always high. In acute myeloblastic leukaemia the scores were always low, and in one case the neutrophils were entirely negative, giving a score of 0. In two cases of acute lymphoblastic leukaemia the scores were high—183 and 202, respectively—and they were also high in 18 cases of chronic lymphocytic leukaemia, thus contrasting specifically with the findings in myeloid leukaemia. While in the past the differential diagnosis between myeloblastic and lymphoblastic leukaemia was academic, it is now of great practical importance because of the use of cortisone for the treatment of lymphoblastic leukaemia. The authors have added another useful observation: whereas in 24 blood smears from 12 patients with Hodgkin's disease the scores ranged from 85 to 258, 16 specimens from 9 cases of lymphosarcoma were all within normal limits, ranging from 14 to 80. In neither condition did treatment influence the initial findings. Dameshek and his colleagues[6] found that the alkaline phosphatase score falls when polycythaemia vera changes into erythraemic myelosis. This can be used to predict leukaemic change.

A possible light on the difference in alkaline phosphatase score between infectious leucocytosis and leukaemic white-cell reaction has been thrown by W. N. Valentine and his collaborators.[7] They showed that leucocyte alkaline phosphatase was increased in a variety of "stressful" conditions, such as acute pyogenic infection, trauma, haemorrhage, and myocardial infarction. Similarly, a distinct rise in the alkaline phosphatase in cells could be induced over a 72-hour period by the administration of large doses of A.C.T.H. or 17-OH-corticosteroids to normal subjects. This pattern of response was absent or greatly diminished in chronic myelocytic leukaemia. The same department[8] has also compared the action of human leucocyte phosphatase on glycerophosphate, adenosine-5′-phosphate, and glucose-1-phosphate. The results were compatible with the hydrolysis of phosphorus being due to the activity of the same enzyme in all three cases.

[1] Gomori, G., *Proc. Soc. exp. Biol. (N.Y.)*, 1939, **42**, 23.
[2] Takamatsu, H., *Trans. Jap. path. Soc.*, 1939, **29**, 492.
[3] Menten, M. L., Junge, J., and Green, M. H., *J. biol. Chem.*, 1944, **153**, 471.
[4] Hayhoe, F. G., and Quaglino, D., *Brit. J. Haemat.*, 1958, **4**, 375.
[5] Kaplow, L. S., *Blood*, 1955, **10**, 1023.
[6] Mitus, W. J., Bergna, L. J., Mednicass, I. B., and Dameshek, W., *Amer. J. clin. Path.*, 1958, **30**, 285.
[7] Valentine, W. N., Follette, J. H., Hardin, E. B., Beck, W. S., and Lawrence, J. S., *J. Lab. clin. Med.*, 1954, **44**, 219.
[8] Follette, J. H., Valentine, W. N., and Reynolds, J., *Blood*, 1959, **14**, 415.

STRONTIUM-90 AT WINDSCALE

A new and disturbing chapter in the history of the 1957 Windscale accident has recently been published. When No. 1 reactor was damaged by an internal fire, radioiodine was released over the surrounding countryside, with consequences that have already been described.[1] It was estimated soon after the accident[2] that 9 curies of strontium-90 and 80 curies of the shorter-lived isotope strontium-89 had also been discharged into the air. The fate of these products is discussed in a report[3] issued jointly by the United Kingdom Atomic Energy Authority and the Agricultural Research Council, and briefly summarized in last week's journal.[4] The quantities involved are not very great in relation to fall-out from distant weapon tests and should not have brought substantially increased contamination of the ground, except perhaps close to the reactor. But this point could not be checked because, until the accident, no detailed measurements of radioactive strontium in soil and vegetation had been made in the Windscale area. Estimates were made of the strontium-90 derived from fall-out in the region affected by the accident (some 200 square miles), with doubtful accuracy, by extrapolation from results obtained in other parts of the country, where systematic sampling and analysis have been undertaken

[1] See *Brit. med. J.*, 1957, **2**, 991 and 1166.
[2] Dunster, H. J., Howells, H., and Templeton, W. L., "District Surveys following the Windscale Incident, October, 1957," International Conference on the Peaceful Uses of Atomic Energy, paper 316, 1958.
[3] Ellis, F. B., Howells, H., Russell, R. S., and Templeton, W. L., *The Deposition of Sr^{89} and Sr^{90} on Agricultural Land and their Entry into Milk after the Reactor Accident at Windscale in October, 1957*, 1960. H.M.S.O., London. Price 5s. net.
[4] *Brit. med. J.*, 1960, **2**, 614.
[5] *Daily Telegraph*, August 17, 1960.

since 1954. Three farms on the coastal plain at distances between 8 and 17 miles from Windscale showed levels of strontium-90 which were (after correction for rainfall variations) about 40% higher on average than in other parts of England. Some of this excess is thought to have been contributed by the accident, but no clear judgment is possible with the uncertain data available.

The report discloses that substantial amounts of radioactive strontium were discharged from the Windscale chimneys before the 1957 accident. An earlier publication[2] referred to "a slight release of radioactivity which was much reduced by improvement of techniques," but this seems to have been an understatement. Three farms within two miles of the reactors were found in late November, 1957, to be quite heavily contaminated by strontium-89 and strontium-90. On average, the deposition was 16 times greater than the level to be expected from world-wide fall-out, and the highest level was 70 times the national average. By measuring the ratio of strontium 89 to strontium 90 the age of a fall-out deposit can be roughly calculated. Tests of this kind showed that the contamination near Windscale came, not from the 1957 accident but from the earlier release of fission products, which, according to a newspaper report,[5] were first noticed in 1955 when fuel elements became overheated while awaiting removal from the reactor. The emission was in the form of particles not completely trapped by the filters in the cooling air exhaust stacks. Milk samples collected from a nearby farm during the three months before the accident contained three times more strontium-90 than samples taken elsewhere. It is disturbing to learn that no surveys of ground contamination were made in the Windscale area, though it was known that strontium-90 was being discharged from the reactor and appearing in locally produced milk. However, there is little to be gained by crying over spilt strontium, so long as the Atomic Energy Authority are satisfied with the adequacy of their present monitoring arrangements.

HAZARDS OF IRON-DEXTRAN

A leading article in the *Journal* of March 12 reviewed the experimental work of H. G. Richmond and of A. Haddow and E. S. Horning, in which they found that the iron-dextran complex "imferon" was carcinogenic in rats and mice. Though recognizing the great value of this compound in the treatment of secondary anaemia, we concluded that the experimental evidence was such as to justify the suspension of the use of imferon in clinical practice, adding, however, the following sentence: "Further, it may well be that imferon has a useful place in the treatment of such cases of iron-deficiency anaemias as are otherwise intractable in the elderly." The manufacturers of imferon subsequently withdrew the drug from the market here, and some time later the Food and Drug Administration in Washington requested the withdrawal of it in the U.S.A. The pros and cons were published in the correspondence columns of the *Journal*, and then after a longish interval a letter from a number of distinguished medical men appeared in the *Journal* of July 16, in which they stated their conclusion that the use of imferon "in the clinical dosage recommended carries a negligible risk, and is probably less hazardous in other respects than intravenous iron preparations and blood transfusions." In their view the use of imferon was justified in the presence of severe iron deficiency and provided iron by mouth could not be employed effectively. In our correspondence columns this week Professor Alexander Haddow, who has been in correspondence with the signatories of the letter in the *Journal* of July 16, says that he is impressed by the considerations they have raised, but states, nevertheless, that no one is justified in asserting that imferon in the clinical dosage recommended carries a negligible risk.

Professor Haddow draws attention to what we believe has been insufficiently stressed in this controversy over imferon—namely, that no one will know what the risk is until something like 15 years or more have passed since the introduction of the substance in clinical practice. It is the long latent period between exposure to a possible carcinogen and the appearance of cancer that lulls people into a sense of false security. If, for example, cancer of the lung appeared a few weeks or months after the excessive smoking of cigarettes, the risk would be brought home dramatically to the profession and to the public. We have already put on record a case in which a secondary tumour appeared at the site of injections of iron-dextran complex. In this week's *Journal* we publish a paper by Dr. J. H. Sturdy and his colleagues from Vancouver, in which they describe the occurrence of a malignant growth in a 74-year-old woman whose anaemia had been treated with six injections of imferon four years previously. The authors of this paper are scrupulously careful not to say this was a direct cause and effect. The possibility of coincidence cannot be excluded, nor do they yet know whether the tumour was primary and not secondary to an-as-yet-undiscovered lesion elsewhere. The time interval between the injection and the appearance of the tumour is again something that must make the careful observer hesitate before making the inference that the tumour was the result of the injection. Incidentally, it would be interesting to know whether the time interval varies with the age of the patient. This case must at least put the medical profession on its guard, especially in the light of the experimental work. As Professor Haddow points out, if the results of animal experiments had been negative they would not unreasonably have been used as indicative of the harmlessness of the preparation. Clearly more experimental work is needed before practitioners could feel justified in using iron-dextran in the treatment of secondary anaemia if the manufacturers were to put the preparation on the market again.

We record with regret the death on August 21 of Sir Harold Graham-Hodgson, consulting radiologist to the Middlesex Hospital, the Royal National Throat, Nose and Ear Hospital, Golden Square, and the Royal Navy.

Drug Treatment of Disease

DRUGS IN THE TREATMENT OF HYPERTENSION*

BY

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There are now many drugs which effectively lower blood-pressure, but the management of the patient with hypertension remains difficult. This is not only because there is, as yet, no agent that will lower blood-pressure predictably and without side-effects, but also because the success of treatment is so often limited by co-existing vascular or renal disease.

Many patients with hypertension do not require drug treatment, and drugs should never be regarded as more than a part of the therapeutic regime. General management remains important, and simple measures such as reduction of weight and the avoidance of excessive mental and physical strain contribute to the well-being of the patient and the reduction of blood pressure. A routine incorporating adequate rest and sleep, with amylobarbitone sodium, 3 gr. (200 mg.) at night, is often helpful. Rigid salt restriction is no longer practised, but the avoidance of table salt and salty foods potentiates the effect of the ganglion-blocking drugs and helps in the control of cardiac failure.

The use of antihypertensive drugs calls for considerable co-operation from the patient. Sympathetic handling by a physician in whom the patient has confidence will make it easier to overcome the difficulties and disappointments associated with this form of treatment. It is desirable for the patient to have some understanding of the disease and of the drugs that he is receiving so that he may recognize hypotensive symptoms and side-effects and take appropriate action. At the same time, the doctor must ensure that the patient has no excessive fears about his blood-pressure and does not worry about the exact level—which is better left untold.

Rauwolfia

The alkaloids derived from the root of *Rauwolfia serpentina* have a moderate hypotensive effect. To some extent this may be due to a tranquillizing action, but there is also a more direct central hypotensive effect. When used alone the rauwolfia alkaloids lower the diastolic pressure by 10 to 20 mm. Hg in some, but not all, patients. They have a more striking effect when used with the ganglion-blocking drugs, which they potentiate. The full fall in pressure may not occur for two to three weeks.

The side-effects are usually minor and include nasal stuffiness, flushing of the skin, diarrhoea, and headache. Muscular pains and rigidity are sometimes complained of, and lactation has developed in some patients. Retention of sodium occurs and may interfere with regimes designed to produce loss of weight. The most serious side-effect is depression. Though not common, it can be severe and in some patients has led to suicide.

There are many preparations available, and various claims have been made that certain of them are free from the more serious side-effects. These claims have not, as yet, been fully substantiated. The preparations in common use are reserpine, "raudixin," and "rauwiloid." Reserpine ("serpasil"), a single alkaloid, is given in doses of 0.1 to 0.5 mg. thrice daily. Raudixin, the refined whole root, is administered in 50-mg. tablets, 3 to 8 a day Rauwiloid, a mixture of alkaloids, is given in doses of 2–4 mg. thrice daily. The use of tablets combining the rauwolfia drugs with other hypotensive agents is unwise. They do not permit the necessary flexibility in treatment, they often contain ineffective amounts of the various constituents, and they prevent assessment of the relative merits of the component drugs.

Chlorothiazide Derivatives

Chlorothiazide and related drugs are chiefly used for their diuretic effect, but they also have a slight hypotensive action. They have a strong potentiating effect when used with ganglion-blocking and adrenergic-blocking agents. The mode of action seems to be through a reduction of plasma volume which accompanies depletion of sodium. The most important side-effects of chlorothiazide therapy are those associated with depletion of potassium, but a few patients complain of nausea and vomiting. Though there are some pharmacological differences between the various derivatives of chlorothiazide available, from the practical point of view there is little to choose between them except on the basis of cost and the size of the tablets.

Chlorothiazide ("saluric") is given in doses of 250 mg.–500 mg. three times a day, hydrochlorothiazide ("esidrex" or "hydrosaluric") 25–50 mg. thrice daily, and hydroflumethiazide ("hydrenox" and "naclex") 25–50 mg. thrice daily. When the chlorothiazide drugs are given every day, as they have to be for treatment of hypertension, it is always advisable to give a supplement of potassium—e.g., 1 g. of potassium chloride thrice daily. When treating patients with ganglion-blocking or adrenergic-blocking drugs, it is dangerous to give chlorothiazide intermittently—for example, two or three days in the week—as this results in large swings in blood-pressure from day to day.

Veratrum Alkaloids and Hydrallazine

The veratrum alkaloids, alkavervir ("veriloid") and protoveratrine ("puroverine," "provell maleate"), cannot be advocated because the effective dose is so close to the toxic dose that vomiting is usually provoked. Hydrallazine ("apresoline") retains a limited place in treatment because of its unique action in lowering blood-pressure and at the same time increasing cardiac output and flow of blood to the kidneys. Unfortunately, side-effects are common and severe. They include headache, flushing, nausea, fever, rashes, and joint pains, and thus disseminated lupus erythematosus may be simulated. Its use is now reserved for those patients in whom the renal function is severely impaired, and it is usually given together with another hypotensive drug. Treatment is

*An article on the "Pharmacology of Hypotensive Drugs," by Dr. M. Harington, appeared earlier in this series (March 5, p. 717).

started with a dose of 25 mg. thrice daily, which may be increased until a total of 300 mg. is being given in the day.

Ganglion-blocking Drugs

These block the ganglia of both sympathetic and parasympathetic systems. The reduction in blood-pressure is only slight when the patient is lying down but becomes considerable in effective doses when the patient is erect. This postural effect is due to the abolition of the vasoconstriction which normally occurs on standing, and to the pooling of blood.

Side-effects from this group of drugs are frequent and are largely due to the parasympathetic blockade. Constipation is almost invariable, and paralytic ileus may occur. The patient must be informed of the importance of regular bowel action and advised on the use of laxatives. Other unpleasant symptoms from this form of treatment include blurring of vision, dryness of the mouth, diarrhoea, difficulty in micturition, and impotence. Neostigmine 7.5 mg. and pilocarpine 3 mg. thrice daily are both of some value in combating these symptoms. Physostigmine drops (½%) help to relieve the blurring of vision, but new spectacles may be necessary. When hypotensive symptoms occur, the patient should lie down and they will usually pass off quickly.

The most frequently used members of this group of drugs are pentolinium, mecamylamine, and pempidine.

Pentolinium ("ansolysen," tablets of 10, 40, and 200 mg.) is a quaternary ammonium compound and resembles hexamethonium. Only a small percentage is absorbed, and the degree of absorption is variable. As a result the control of the blood-pressure may be erratic. Treatment should be started with 20 mg. thrice daily, each dose being taken at least one hour before a meal. The dose may be increased every two or three days. Eventually a total daily dose of about 600 mg. is usually required.

Mecamylamine ("inversine," tablets of 2.5 mg. and 10 mg.) is a secondary amine, and has the advantage of being regularly and completely absorbed. It has a prolonged action, which can be a disadvantage when there are side-effects. It has a distinctive side-effect in producing neurological signs—particularly tremor—but this is uncommon. It is usually wise to begin with 2.5 mg. twice daily (e.g., at 7 a.m. and 5 p.m.) and then gradually increase the dose until the drug is being taken four times a day. The eventual dose is commonly between 40 and 80 mg. a day.

Pempidine ("perolysen," "tenormal," tablets of 1, 5, and 10 mg.) is a tertiary amine and closely resembles mecamylamine except that its action is not as prolonged, and, it is claimed, it does not give rise to neurological signs. Treatment may be started with 2.5 mg. twice daily and gradually increased until it is being taken four times a day.

When starting therapy with the ganglion-blocking drugs, frequent recordings of the blood-pressure are necessary, and for this reason treatment is best begun in hospital. In assessing the drugs the patient's blood-pressure should be recorded first in the recumbent position and immediately afterwards when he stands erect. The aim should be to maintain the diastolic pressure below 100 mm. Hg in the erect position. Minor dizziness may have to be tolerated if the blood-pressure is to be satisfactorily controlled, but faintness calls for a reduction in dosage. When troublesome side-effects are occurring without an adequate fall in pressure, rauwolfia or chlorothiazide should be added and the dose temporarily halved, and then gradually increased to the necessary level. Tolerance develops to all these drugs, and the doses may have to be increased for some weeks or even months after treatment has started.

Though treatment with the ganglion-blocking drugs may be complex and unpleasant, it has been possible to achieve satisfactory control of blood-pressure in many patients without producing undue discomfort. In such cases there is no indication to change to the more recently introduced adrenergic-blocking drugs.

Adrenergic-blocking Drugs

The recent introduction of drugs that will selectively block the peripheral sympathetic nervous system has been a major development in pharmacology but of still unproved value in therapeutics. These drugs do not affect the ganglia, and no paralysis of the parasympathetic system occurs. The hypotension which they produce is largely orthostatic, and the fall in pressure is even greater on exercise. Hypotensive symptoms are common and may be severe, particularly on exertion. Strenuous effort should therefore be avoided.

Side-effects occur occasionally and are relatively slight. They include nasal stuffiness, parotid pain at meal-times, muscular weakness, exertional dyspnoea, diarrhoea, and impotence. The diarrhoea can usually be relieved by propantheline ("pro-banthine") 15 mg. thrice daily. There is good evidence that hypertensive patients with nitrogen retention are more readily precipitated into uraemia by these drugs than by the other hypotensive agents. For this reason some physicians have already abandoned their use.

The two drugs of this group in current use are bretylium tosylate and guanethidine.

Bretylium tosylate ("darenthin," 200-mg. tablets) is absorbed irregularly, and large swings of pressure may occur. The effect starts in about 1–2 hours and lasts from 4–8 hours. It is customary to begin treatment with 100 mg. thrice daily, each dose being taken after a meal. Some patients develop hypotension with as little as 50 mg. Initially, several recordings of the blood-pressure each day are desirable. 100 mg. may be added to each dose until an adequate response has been obtained.

Guanethidine ("ismelin," tablets of 10 and 25 mg.) differs from bretylium in that its hypotensive action lasts for two to four days with a transitory peak of effect at about four hours. This means that doses are additive from one day to another, and the full effect of a particular daily dosage will not be appreciated for about three days. Because of this prolonged action, smoother control of blood-pressure is obtained, but when hypotensive symptoms develop they take a long time to abate. Treatment should be started with 10 mg. once daily, and the dose increased not more frequently than every four days by 10 mg. at a time. Most patients require from 30 mg. to 60 mg. daily, which is best given in divided doses.

Tolerance develops with both bretylium and guanethidine, and a gradual increase of dosage may be necessary for several months. This has proved a serious disadvantage with bretylium, because the number of tablets required may become excessive and because treatment may suddenly become ineffective. As with the ganglion-blocking drugs, rauwolfia and chlorothiazide

potentiate their action. If these drugs are to be added to the adrenergic-blocking drugs, the dose of the latter should first be halved and then gradually increased.

Indications for Drug Therapy and the Choice of Drug

A large number of patients with high blood-pressure need no antihypertensive drug. Systolic hypertension alone can be ignored—except as evidence of vascular sclerosis—and diastolic hypertension must be persistently raised above 100 mm. Hg before drug treatment has to be considered. Remediable conditions such as phaeochromocytoma, coarctation of the aorta, and unilateral renal disease must be looked for and treated.

The severity of the hypertension must be assessed, with particular attention given to the state of the heart, brain, ocular fundi, and kidneys, before treatment can be planned. Middle-aged women and the elderly often tolerate high levels of pressure for years without mishap, and if there is no evidence of secondary cardiac or renal damage, and if the retinal examination reveals no exudates, haemorrhages, or papilloedema, energetic drug treatment need not be given. Younger patients with labile hypertension and no evidence of vascular deterioration usually require no more than small doses of phenobarbitone.

At the other end of the scale are those patients in whom the lowering of the blood-pressure is of the greatest importance. If there are retinal signs of papilloedema, soft exudates, or haemorrhages, or left ventricular hypertrophy with failure associated with a diastolic pressure of 120 mm. Hg or more, then vigorous treatment is imperative. Provided that renal function is not severely impaired and there has been no recent myocardial infarction, guanethidine is probably the drug of choice, though it yet remains to be proved that its long-term use in the severest grades of hypertension (malignant hypertension) is as beneficial as mecamylamine. When cardiac failure is present, the addition of chlorothiazide with potassium supplements will serve the double purpose of providing a diuretic and potentiating the hypotensive effect. In those without evidence of coronary, cerebral, or renal vascular disease, the diastolic pressure should be reduced to about 90 mm. Hg when the patient is standing. In the older patient and those in whom there are other signs of vascular disease, a fall to 100 to 110 mm. Hg is safer and may be adequate.

In a less serious state but still requiring control of blood-pressure are those patients in whom the hypertension has led to left ventricular enlargement, as shown on physical examination or electrocardiographically, renal damage, as shown by albuminuria or a rise in the blood urea, or episodes of cerebral thrombosis or haemorrhage, or is undoubtedly progressing. In some of these cases rauwolfia or chlorothiazide alone may be sufficient, but in many the more powerful adrenergic-blocking or ganglion-blocking drugs are necessary.

Hypotensive drugs must be used cautiously when there are signs of coronary or cerebral vascular disease or evidence of renal failure. Lowering of the blood-pressure can lead to coronary and cerebral thrombosis and to uraemia, yet the persistence of high blood-pressure increases the dangers of cardiac and renal failure and of cerebral haemorrhage. There is no solution to this dilemma, but the wisest course of action is to lower the blood-pressure cautiously, with special care being taken to avoid hypotensive episodes. Rauwolfia or chlorothiazide should be employed in the first place, but, if these prove inadequate, treatment should be started with guanethidine or, perhaps, mecamylamine. No attempt should be made to achieve normotensive levels, and one must be satisfied with a diastolic pressure of 100–110 mm. Hg.

There remains a group of patients in whom the blood-pressure is persistently raised but who show little or no evidence of harmful effects from it. Some physicians feel that high blood-pressure on its own should not be treated and that one should await the signs of hypertensive disease before subjecting patients to the hazards of the antihypertensive drugs. On the other hand, there is no doubt that many patients in the younger age groups with isolated hypertension will eventually develop irreversible changes in their blood vessels and kidneys as a result of the raised diastolic pressure. If the blood-pressure can be brought down safely and without discomfort, then it seems right to do so, but, as yet, no drugs can be relied upon to do this in every patient. It is worth trying rauwolfia or chlorothiazide initially, and, if they fail, then guanethidine or mecamylamine. If it is impossible to achieve a satisfactory fall in pressure without side-effects or hypotensive symptoms, then it is probably best to abandon drug treatment for the time being.

Conclusion

In spite of the frequency of side-effects and of hypotensive symptoms, satisfactory control of the blood-pressure can be achieved in most hypertensive patients. In the milder cases, rauwolfia and chlorothiazide are the drugs of choice. In the more severely affected patients guanethidine or mecamylamine should be tried. One or other will usually produce an adequate fall in pressure with few undesirable effects. With the careful use of the drugs described, the prognosis of patients with hypertension is improved and their symptoms are usually relieved.

AMENDMENTS TO BRITISH NATIONAL FORMULARY, 1960

Hydrocortisone and Neomycin Ear-drops

The formula was, at the time of publication, identical with that of two proprietary preparations. One, Hydromycin Ear-drops, which was supplied in packs containing 3 ml., has recently been replaced by Hydromycin D Ear-drops containing prednisolone instead of hydrocortisone acetate. The other preparation, Neo-Cortef Ear-drops, is supplied in 5 ml. packs. The two editions are, therefore, amended as follows:

Standard Edition

Page 74. Aurist. Hydrocort. et Neomyc.
Amend the quantity to be dispensed unless otherwise directed from 3 ml. to 5 ml.

Additions

Page 7. Amend Hydromycin Ear-drops to Neo-Cortef Ear-drops.

Proprietary Preparations

Page 214. Delete reference to Hydromycin Ear-drops.

Alternative Edition

Page 174. Hydrocortisone and Neomycin Ear-drops.
Amend 3 ml. to 5 ml.

Additions

Page 8. Delete Hydromycin Ear-drops.

Proprietary Preparations

Page 240. Delete reference to Hydromycin Ear-drops.

Corrections

Standard Edition

Page 9. *Amendments to Composition.*
Add Elix. Chloral. pro Inf.
Page 84. Crem. Calam.
Amend Water, 465 gr. (approximate percentage 49); to Water to 960 gr. (approximate percentage to 100).
Page 148. Tab. Acetazolam.
Add B.P. to English title.
Page 221. Amend Sinacthar to Sinaxar.
Page 220, 228. Amend Raspenyl to Respenyl.

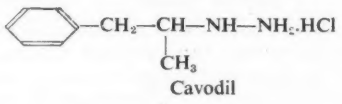
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

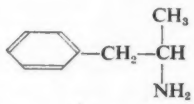
Pheniprazine

"Cavodil" (Benger Laboratories).

Chemistry.—This drug is the hydrochloride of β-phenyl isopropyl hydrazine and has a chemical similarity to amphetamine:



Cavodil



Amphetamine

Pharmacology.—The enzyme monoamine oxidase plays an important part in the destruction of serotonin (5-hydroxytryptamine) when it has been released from nervous and other tissues. A number of substances have been found to inhibit the action of monoamine oxidase and thus allow the accumulation of serotonin. Some monoamine oxidase inhibitors have been found beneficial in the treatment of primary depressive states, and it is possible that the accumulation of serotonin is connected with this therapeutic effect, especially as reserpine, which causes the depletion of serotonin stores, appears occasionally to produce depression.

β-Phenyl isopropyl hydrazine is a potent monoamine oxidase inhibitor and appears to exert its action selectively on the brain. Its effect has been detectable for six days after administration. It is because of these actions that it is thought to exert an antidepressive effect.

Therapy.—The drug has principally been given for uncomplicated primary depression. About half the patients tried on it have improved. It seems unlikely that it is as effective as E.C.T. in the treatment of depression. One author administered it to a number of children with severe emotional disorders, and noted improvement in about a third. Sleeplessness proved a frequent and troublesome side-effect here, however. The initial dose should be 12 mg. once daily for not more than 14 days, the amount then to be decreased as the patient improves. This is less frequent administration than is required for other antidepressive drugs.

Side-effects.—Orthostatic hypotension is the most frequent side-effect. Jaundice and a fall in the leucocyte count have been reported. One curious finding has been a loss of red–green colour discrimination, which was restored when the drug was withheld. This drug should not be given to patients with liver damage, blood disease, or organic disease of the nervous system. It potentiates the effect of other sedative drugs.

N.H.S. Basic Price.—3-mg. tabs., 100 for 30s.

The Classification of Pharmaceutical Preparations, Survey of Comparative Health Legislation describes the various systems of classification of pharmaceutical preparations in ten or more countries, and brings out the divergences in their different regulations for controlling preparations which may be dangerous. (Offprint from *International Digest of Health Legislation, Geneva,* vol. 11, No. 1, 56 pages; published in English and French. Price 3s. 6d., obtainable from H.M.S.O., P.O. Box 569, London, S.E.1.)

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Dilemma of Implant Surgery

SIR,—As chairman of the committee which for four years has been working upon the possibilities of standardization in the design and materials of metal surgical implants, I welcome your leading article (August 13, p. 516) upon this subject. The regulation of surgical materials has until recently lagged far behind *materia medica,* for which there are official pharmacopoeias and national formularies. In this country we can take a certain amount of credit for having advanced so far, through the good offices of the British Standards Institute, which has provided the means of setting up reliable standards in so many of the needs of the surgeon (instruments, splints, and hospital equipment). Few, if any, countries have achieved as much. Nevertheless, there is a great deal more remaining to be done, particularly in this field of surgical implants, where mechanical efficiency has to be married with biological compatibility. All these matters are well dealt with in your article.

Here I would like to qualify one statement that you make. This refers to a comparison between implants made from cobalt-chromium alloys and those from stainless steel. Lest anyone should feel that the use of the latter provides some serious risk, it should be noted that the work of Scales *et al.*[1] emphasized particularly the risks of certain types of stainless steel formerly employed but not now used by British manufacturers of surgical implants. These risks especially arise when implants of stainless steel having different compositions are mixed together in the body. The evidence we have is that stainless steel of nickel-chrome-molybdenum ferrous alloy (18/8 SMo), or, as it is known in British Standards, En 58J, has a negligible risk in this matter of corrosion, provided it is not mixed with other ferrous metals. Compared with cobalt-chrome alloy it appears to have some mechanical advantages: certainly it is more amenable to machine working in manufacture, and of course it is more readily available at lower cost in this country. For most purposes there is no indication for a general movement away from the use of the correct type of stainless steel.—I am, etc.,

Exeter, Devon. NORMAN CAPENER.

REFERENCE

[1] Scales, J. T., Winter, G. D., and Shirley, H. J., *J. Bone Jt Surg.*, 1959, **41B**, 810.

"Imferon" and Cancer

SIR,—Respect must be paid to the views and experience of Dr. J. J. R. Duthie and his co-signatories, expressed in their letter of July 16 (p. 234). Meantime I have had the advantage of some correspondence with them. It is obvious, and accepted, that the administration of a great many drugs in common use is a calculated risk, when the hope or certainty of immediate benefit has to be weighed against the possibility of later toxic effects. But I have been specially impressed by various considerations they have raised in the particular case of "imferon": for example, that many patients correctly so treated have disease of the alimentary tract reducing their life expectancy to well below a

latent period within which any carcinogenic hazard is improbable; or, secondly, that no advantage is to be achieved in withholding imferon from patients with unquestionably refractory iron-deficiency anaemia, if they are left without effective treatment, or given therapy carrying an immediate and known hazard, as from intravenous iron or transfusions.

Having said this, I am, however, quite certain that no one is justified in asserting at the present moment, as the authors do, that the use of imferon in the clinical dosage recommended carries a negligible risk. From the nature of the case we cannot have a useful answer to this question under something of the order of 15–20 years. The statistics of the hazard (if indeed it exists in man) are quite unknown. We cannot therefore say it is negligible.

The letter also raises another question. If the results of experimental work with imferon are in practice to be disregarded as an indication towards policy in man, what evidence from experimental work would be acceptable as justifying either the prudent withdrawal of a given preparation or at least a warning statement? Although the results of animal experimentation are immensely valuable in this kind of problem, they can never be regarded as more than an approximate guide. Agreed that we cannot extrapolate with any certainty to man, it will also be agreed that had the results of animal experimentation with imferon been negative they would certainly (and not unreasonably) have been used as indicative of the preparation's harmlessness.

On balance, I believe all the work on imferon originating from H. G. Richmond's most interesting observation, and extended in other papers and correspondence, has been profitable. It appears that the preparation had been used in very many cases without adequate indication, or indeed almost indiscriminately; and a useful result may be considerably to reduce its administration to younger age-groups, and to patients capable of responding perfectly satisfactorily to other means.—I am, etc.,

Chester Beatty Research Institute, London, S.W.3. ALEXANDER HADDOW.

Artificial Insemination

SIR,—Dr. A. Torrie (August 6, p. 470) upbraids the Faversham Committee on A.I.D. for giving "conclusions on insufficient data." Specifically, he suggests that the evidence of marriage guidance cases shows that husbands subscribing to A.I.D. are the type more likely to become good fathers than those assisted by A.I.H.

Does not Dr. Torrie overlook two facts? First, in A.I.D. the husband simply is *not* the biological father. However impressive his qualifications for the paternal role may be in every other respect, this fundamental flaw places him under a heavy handicap. Secondly, the interests of the child must be paramount at all times. Surely no one who recognizes the grave hazards to the child in A.I.D.[1] could prefer donor insemination to A.I.H. I know of no practitioner in A.I.D. who would do so.

Let us be quite clear about this. There is a sharp distinction between A.I.H. and A.I.D. Provided A.I.H. is grounded upon sound medical indications, including psychological suitability, and safeguarded by skilled technique, it presents a logical extension of the assistance which a doctor may offer to childless couples. Legally, it poses no serious problems. Psychologically, despite a measure of depersonalization, it gives a real sense of fulfilment. Morally, it is a proper attempt to further the procreative end of marriage.

Whatever the merits of the case for A.I.D., the arguments in its favour are scarcely so comprehensive or well supported.—I am, etc.,

Irvine, Ayrshire. ALEXANDER W. MACARA.

REFERENCE

[1] Report of the Departmental Committee on Human Artificial Insemination, 1960, p. 46. H.M.S.O.

Mental Health

SIR,—The present Mental Health Year has initiated a lot of lectures, discussions, and published statements on psychiatry and on the mental health in persons, families, and communities, but special note might well be made of two outstanding contributions, coming, perhaps significantly enough, from distant parts of the world.

I refer first to the extremely thoughtful and comprehensive statements (July 30, p. 345) by Professor Tsung-yi Lin, of Formosa. Therein is a clear perception of the changing attitude and method towards the urgent need for the medical student to obtain sound education in mental health, a "programme which may, and will, change in accordance with the scientific evolution and the needs and resources of the time." Surveys in Formosa have yielded a clear picture of the prevalence of mental disorders in the community in which the *great majority of patients were cared for at home.* Hence the emphasis which Professor Tsung-yi Lin and his departmental team place on not to concentrate (only) upon training an inevitably small number of specialists, but to guide the future doctors in understanding and forwarding the mental health programme and to instruct them to treat mild psychiatric problems competently, the teaching of the matter being "as a part of the basic philosophy of medical education in presenting the concepts of man as a bio-psycho-social unit and of sound doctor–patient relationships."

This might be read in conjunction with the letter of Dr. G. R. Davies (p. 390), who discusses some of the necessary practical interrelations of those interested in social psychiatry as opposed to individual psychiatry, and particularly the interesting yet quite realistic suggestion that the recognition of the troublesome psychopath may have become even more crucial than the detection of, say, a paratyphoid carrier. The teacher has a remarkable responsibility when it is noted that a child from the ages of 5 to 15 years spends 13,000 hours in school classes. However, we should not be invidious in regard to who plays dominant parts in the work for mental health. Parents, teachers, social workers, and doctors all have a significant place in the teams. There ought to be a diminishing truth in the suggestion that the medical profession lies in some danger of being outstripped by lay and non-medical organizations in advocating social reforms which have a direct bearing on mental health.

In the Beattie–Smith Lectures[1] by Professor W. H. Trethowan in Sydney (the second source of inspiration in this Mental Health Year), a plea is made against any further propagation of the absurd "mind–body dualism" which so strongly colours the thinking of many practitioners, and persistently interferes with the adequate appreciation of man as a totality. Trethowan reflects and enlarges upon the idea that perhaps it is the investigation of man's nature which is the "area of medicine's main neglect."

I suggest that, while so many conferences are being held on present trends in the teaching and practice of psychiatry and mental health, and the likelihood of rapid advances and change in respect to these in undergraduate and postgraduate schools, the clear and informative writing of Tsung-yi Lin and W. H. Trethowan should be kept in mind. To some of us it is a happy thought that the fuller purpose and needs in mental health is being revealed all over the world.—I am, etc.,

Department of Child Health, University of Bristol. A. V. NEALE.

REFERENCE

[1] Trethowan, W. H., *Med. J. Aust.*, 1960, **4**, 441, 481.

Imaginary Poverty

SIR,—I was greatly interested in Dr. A. W. Beatson's letter on this subject (August 6, p. 468), as I have recently had a case exactly similar to those he describes in this mainly residential suburb where elderly people living alone in pseudo-poverty seem to be rather common.

Following on the death of her husband this old lady passed the last few years of her life in veritable filth and squalor despite a £14,000 legacy left to her by that gentleman. An interesting sidelight to this case was that the patient was cared for during the daytime by another elderly lady who shared the delusion of poverty completely and in a most naive manner, though she was intellectually well aware of the real financial circumstances of her mistress—surely a very unusual variety of *folie à deux*!

I agree that treatment would appear to be very difficult, but I suggest a rather firm attack via the family solicitor might produce the best results.—I am, etc.,

London, S.W.13. H. LANTIN.

SIR,—The disease of "imaginary poverty" as described by Dr. A. W. Beatson (August 6, p. 468) is no more nor less than the true depressive psychosis, of which Dr. Beatson gives a good description of some of the classical symptoms. In Bleuler's[1] early description of the depressive psychosis he pointed out that the delusions were usually concerned with three themes—namely: (1) delusions of disease, (2) delusions of sin, (3) delusions of poverty. It is perfectly true, as Dr. Beatson states, that delusions of poverty only affect the well-to-do. Concern with poverty when one *is* poor can hardly be called a delusion. Nor is it so manifestly absurd and obvious as when it occurs in the financially better off.

Often it is difficult to recognize this mental illness as a depression. As I have stated elsewhere,[2] the term "depression" is not descriptive of the mood as the normal person knows it. It is different from the normal despondency which we all know. The mood has a special and abnormal quality, so that very frequently these patients do not admit to feeling depressed at all. Instead, they have the depressive type of delusions, they may be agitated or retarded, and they awaken in the early mornings to ruminate about their imaginary poverty or sins or hopeless future, blaming themselves for it all. I need hardly remind Dr. Beatson that there is an excellent treatment for this illness—namely, E.C.T. —I am, etc.,

London, W.1. S. BOCKNER.

REFERENCES

[1] Bleuler, E., *Lehrbuch der Psychiatrie*, 1916. Berlin.
[2] Bockner, S., *Med. Press*, 1960, **243**, 175.

Psychiatric Terminology

SIR,—Dr. E. B. Strauss's address "The New Tower of Babel" (July 16, p. 224) raises a matter of immediate topical interest. In the near future tribunals will be set up under the Mental Health Act to consider the dispersal of mental cases. The majority of the members will not be practising psychiatrists but will have to consider the evidence of psychiatrists who will be forced to use psychiatric terminology.

It is too much to hope that a set of definitions can receive universal acceptance within the next few years, and during these years the mental health tribunals may be misled by the varying meanings of the terms used. What is needed is not a glossary of what the terms should mean, but a glossary giving the various meanings that the various schools of psychiatry give to these terms. Such a glossary would enable the non-psychiatrist members of the tribunal to ascertain the real meaning of the evidence given to them.—I am, etc.,

Petworth, Sussex. W. ANTONY BALL.

New Rashes for Old

SIR,—I would like to thank Dr. Joan B. Landsman and her colleagues, of Glasgow, for their interesting and helpful account of the "new rash" (August 6, p. 464).

During the last week in July and the first week of August, in a rural Shropshire practice, I have seen six young patients with this very same rash and its accompanying clinical features. The ages of five of the patients varied from 12 months to 11 years, but the oldest was a housewife of 34. The blotchy, bright pink, maculo-papulo eruption of the face was present in three of the cases (two baby boys and a little girl of 4). These also had the tiny, discrete papules (best seen in reflected light) on the limbs and trunk which Dr. Landsman describes, and which were common to the other three patients. In every case the rash was not irritating, and three of the affected children's mothers volunteered the information that it was "under the skin." The older children and the housewife complained of headache and nausea, and of feeling generally "unwell." The babies were "off their feeds" and tearful. It seems that the rash appeared a day or two after the onset of the constitutional symptoms. The average temperature, taken when the patient was first seen in the surgery or at home, was 99.6° F. (37.5° C.). The highest temperature noted was that of a girl of 11; it was 102° F. (38.9° C.) She had a very bad sore throat and grossly enlarged tonsils, whereas the others merely had a mild cervical adenitis. This fact may set her apart from the others as far as the diagnosis is concerned, but her rash was identical to theirs. As she was a temporary resident, and returned home before she was quite well again, I have not heard how she is getting on. The other patients recovered completely in three or four days, and so far there have been no complications.

The epidemiology of five of the cases is of some local interest, in that three of these, including the housewife, live in the same road and are in frequent contact, and they, in their turn, are in the habit of visiting or being visited by the other two, who live at the other end of the town. Unfortunately, no throat or rectal swabs have been taken, and there have not yet been any other cases. —I am, etc.,

Much Wenlock, Salop. J. PARTON.

Serum Detection of Carcinoma

SIR,—The article by Drs. Earle Hackett and Edith Gardonyi (June 11, p. 1785) reporting their experience in the serum detection of carcinoma by the Schultz–Dale technique, as described by us earlier[1 2] and as confirmed by Dr. D. Burrows,[3] is of real interest to me. Drs. Hackett and Gardonyi emphasize that they publish the present account because it offers "further confirmation . . . of the two main features" of our work. But, while they have confirmed the specific immunologic nature of the phenomenon we described, they did not confirm our findings that such a phenomenon could be utilized as a diagnostic test for carcinoma.

In going over the details of the method that Drs. Hackett and Gardonyi have used, I find a few points of divergence in technique and in interpretation from our original method which, I believe, could easily explain this quantitative difference between their results when contrasted with our own findings and those of Dr. Burrows. The most important variation which Drs. Hackett and Gardonyi have introduced is the time allowed for the reaction to take place. These investigators allowed only 30 seconds for contact of the serum with the sensitized horn, while we allow five minutes.[1] Drs. Austen and Brocklehurst[4] have recently shown that anaphylactic release of histamine from sensitized guinea-pig tissues begins within 15 seconds of antigen addition and reaches a maximum rate within 100 seconds. Thus the 30 seconds time limit seems (to us) to be inadequate from both theoretical and practical considerations. This short period of exposure would, of course, exclude all the delayed contractions which in our experience are significant provided they are the requisite height. Dr. Burrows has also emphasized this aspect.[5] This would mean that the sera from carcinomatous patients which give rise to delayed positive reactions (which we include as positive tests) have been labelled as negative.

Furthermore, the tests labelled by Drs. Hackett and Gardonyi as "inconclusive" should have been regarded by them not as failures, but rather as partial successes or as weak positive tests—since in all these tests an additional antigen (not shown in the control horns) was detected in some (but not all) of the carcinoma sensitized horns after these were desensitized to normal serum (indicating the carcinomatous nature of these reactions). Drs. Hackett and Gardonyi rightly emphasized that "if the reliability claimed by Makari and Burrows could be reproduced in a few more centres the test would be worth setting up, in spite of its technical difficulties, in all major medical laboratories."

I am sure that Drs. Hackett and Gardonyi would like to know that just this past week Dr. W. H. Hauss, Director of the Internal Medicine Clinic at the University of Munster in Germany, has reported on his two-year experience with this test on 120 patients.[6] He stated that "the Makari serologic test for cancer has at least 90% positive accuracy." Gordilowa, Kiesielewa, and Malyszewa,[7] at the Cancer Institute in Moscow, also used the Schultz–Dale test (referred to by them as the anaphylactic reaction *in vitro*) for detection of specific antigens in the blood serum of patients with malignant neoplasms. They also utilized the blood serum of healthy subjects for desensitization. Their results also confirm our claim that the serum of subjects with malignant tumours contains a specific antigen which is absent in people suffering from other diseases and in healthy persons. Grace and Lehoczky,[8] at Roswell Memorial Park Institute in Buffalo, N.Y., using the Schultz–Dale test, again confirmed our earlier findings[2] of the presence of antigenic differences between tumorous and normal tissues.

Further confirmation of the usefulness of this approach came from Professor Baruah,[9 10] who, using our method, was able to demonstrate elegantly the presence of an antibody to a tumour antigen in a transplanted tumour-bearing animal. Shevaliagin,[11] working at the Institute of Epidemiology and Microbiology of Moscow, and utilizing this same method (of anaphylaxis with desensitization *in vitro*), has also presented evidence for the specificity of antigens found in the blood plasma of rabbits with Brown–Pearce carcinoma.

In closing, we wish to congratulate Drs. Hackett and Gardonyi on their excellent contribution to this field. Their studies on non-specific contractions and on the effectiveness of pooled human serum for the desensitization of normal antigens are particularly important. Their rigid system of controls which enabled them to confirm the immunological basis of our method is also basic. I am confident that, with the suggestions I have offered herein, the sensitivity of their system will be further improved.—I am, etc.,

Muhlenberg Hospital, Plainfield, N.J., U.S.A. JACK G. MAKARI.

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1 Makari, J. G., *Brit. med. J.*, 1955, **2**, 1291.
2 —— ibid., 1958, **2**, 358.
3 Burrows, D., ibid., 1958, **1**, 368.
4 Austen, K. F., and Brocklehurst, W. E., *Nature (Lond.)*, 1960, **186**, 866.
5 Burrows, D., *Brit. med. J.*, 1960, **1**, 58.
6 Hauss, W. H., *Med. Tribune*, 1960, **1**, 12.
7 Gordilowa, W. W., Kiesielewa, E. S., and Malyszewa, S. F., *Nowotworry*, 1959, **9**, 261.
8 Grace, J. T., jun., and Lehoczky, A., *Surgery*, 1959, **46**, 238.
9 Baruah, B. D., after Green, H. N., *Ann. N.Y. Acad. Sci.*, 1957, **68**, 285.
10 —— *Nature (Lond.)*, 1958, **181**, 624.
11 Shevaliagin, V. J., *Vop. Onkol.*, 1959, **5**, 149.

Doctors' Letters

SIR,—I have every sympathy with Dr. Kenneth Lancer (August 13, p. 540), but his amusement is surely falsely based. It is, or should be, no business of a casualty officer to sort out diagnostic riddles. Were he confined to dealing with casualties, where his skill in riddles will be fully employed, perhaps he would find time to write a brief note letting the family doctor know what has been done, and what any *x*-rays have shown; not least what he himself thinks. Whether the patient has been referred by his own doctor or not, he will almost inevitably see him afterwards.—I am, etc.,

Bishop's Stortford. R. J. BENNISON.

SIR,—I was very interested in Dr. John Fry's letter (July 30, p. 384), and agree entirely with what he says. I am unable to agree with Dr. Kenneth Lancer's conclusions (August 13, p. 540), though I do sympathize with his difficulties.

In my department I personally answer all doctors' letters. For this purpose I have a secretary each morning, and she is able to cope with the 20 or 30 letters a day. I make no attempt to write letters to doctors about patients who arrive without a doctor's letter. I am unable to write to these doctors for two reasons; firstly, I have not sufficient secretarial help (this could be rectified); secondly, and much more important, we find that a very large proportion of the patients do not know the name of their doctor, and, if

they know the doctor's name, they are very often unable to give his address.

I feel that we should write to doctors about all patients we see, but I can see no way of overcoming the second difficulty. If anybody could suggest how to overcome this difficulty, I would be interested.—I am, etc.,

St. James' Hospital, London, S.W.12. DAVID CARO.

Side-effects of Phenindione

SIR,—I read with interest the two articles (August 13) on the side-effects of phenindione by Dr. Norman Jones (p. 504) and Drs. Gordon Mather and Clifford Riley (p. 506). Of approximately 100 patients who have started treatment with phenindione in the past six months at St. Thomas's Hospital, three patients have had to have the drug discontinued because of severe side-effects. These were: (1) an exfoliative dermatitis, (2) persistent diarrhoea and vomiting, and (3) agranulocytosis and fever.

Thus, in this group of patients a 3% incidence of side-effects has been encountered. It is felt that attention should be drawn to this risk as outpatient and long-term anticoagulant therapy becomes more common.—I am, etc.,

St. Thomas's Hospital, London, S.E.1. R. W. PAYNE.

Prevention of Post-operative Oedema

SIR,—The article entitled "The Prevention of Post-operative Oedema," by Mr. James Calnan and Mr. A. Barr (July 23, p. 261), describes a clinical trial of "chymar," lyophilized chymotrypsin, carried out by three surgeons. The conclusions that "chymar . . . has no material effect on the degree or incidence of post-operative oedema or bruising" was reached after treatment of 56 patients for 48 hours only. Treatment for a longer period would convince the authors that the oedema of the face, particularly following cosmetic operations, in those patients treated with chymar has for practical purposes resolved in all but a small percentage in five days. This factor is especially important to the private patient, who may have as much as five days as an in-patient. The American observers confirm my own views that there is little difference in the patients treated with chymar and the controlled series at the end of 48 hours.

Fourteen patients in the series treated were given a general anaesthetic supplemented by a local anaesthetic —surely a combination which gives poorer results than local anaesthesia or hypotensive anaesthesia alone.—I am, etc.,

Queen Victoria Hospital, East Grinstead. F. T. MOORE.

Rehabilitation of Long-stay Mental Hospital Patients

SIR,—In their interesting paper (August 6, p. 436) on the discharge and after-care of long-stay mental hospital patients, Dr. J. C. N. Tibbits and Mr. W. B. Harbert say, I think rightly, "What is here described as a specially arranged investigation should be part of the routine work of psychiatrist and social worker." I should have been interested, however, to learn more of the criteria they found useful in selecting patients as fit or not for discharge.

My own experience is that this is often a difficult prognostic exercise. Not only does one sometimes select the wrong patient for discharge but conversely it seems almost certain that one leaves unselected others who would, in fact, with adequate rehabilitation have become fit for discharge. This point was emphasized to me fortuitously when, because of the enforced closing of two wards, a number of patients from a closed ward for chronic psychotics had temporarily to be housed in a rehabilitation ward. In point of fact, several of these same patients improved in social behaviour, lost residual psychotic symptoms, were found suitable employment, and were successfully discharged within a matter of months.

In the routine reviewing of the needs of long-stay mental patients I do not think the psychiatrist and social worker can do more than make a broad estimate of the "rehabilitation potential" of each patient: that is, the extent to which the mental state and/or social circumstances determining his dependence on mental hospital are susceptible of change *with planned rehabilitation*. If that estimate is favourable, our own practice is to admit the patient to a rehabilitation ward providing an optimal environment for further progress to independence. Here the programme includes re-establishing contacts with relatives, encouraging visits and leaves, ward community meetings, resettlement conferences, and well-paid group and individual work outside the hospital. With this regime a number of patients can eventually be discharged whose mental state at initial review would have seemed to make resettlement in the community impossible.

My impression is that the successful rehabilitation of patients who have spent up to half their lives in a mental hospital must be a slow process, occupying many months in hospital while the mental state of the patient and the acceptance of the community both have a chance gradually to improve. I would add, in conclusion, that I completely endorse Dr. Tibbits's and Mr. Harbert's comments on co-operation between social worker and psychiatrist, adequate after-care, and the need for suitable hostel accommodation.—I am, etc.,

Roundway Hospital, Devizes, Wilts. M. A. T. WATERS.

Tetanus Prophylaxis

SIR,—It is the view of most authorities that anti-tetanus serum need not be used if the patient has been actively immunized with tetanus toxoid. I read with amazement, therefore, in Hale-White's *Materia Medica, Pharmacology and Therapeutics*,[1] that "a protected [with tetanus toxoid] individual should, nevertheless, if the subject of extensive and dirty wounds, be given a prophylactic dose of anti-tetanus serum."

At the present time the casualty officers at the Hull Royal Infirmary and at the Victoria Children's Hospital, Hull, are using anti-tetanus serum when there is no certain evidence of the patient having received a course of tetanus toxoid. The patient (or parent) is given a letter from myself which is to be handed to the patient's general practitioner. In it I state:

"Your patient has received a dose of anti-tetanus serum to-day. If, in the future, a further dose of A.T.S. was to be given it is probable that it would be rapidly eliminated from the circulation because of the formation of antibodies to the globulin contained in the first injection. The second injection would, therefore, probably be quite useless, and at least one patient has died of tetanus after such a second dose of A.T.S. (Reference: Littlewood *et al.*, *British Medical Journal*, 1954, **2**, 444).

"It is, therefore, of great importance that your patient should be actively immunized with tetanus toxoid. This procedure obviates the need for anti-tetanus serum at any

future date. The course should be started six weeks after the A.T.S. injection, but if it must be started earlier than this it should be given at a different site to the A.T.S. injection, and as long as possible afterwards. This may give a lower antigenic response, however.

"A card has been given to the patient which should be completed by the doctor giving the injections. Children immunized early in life against tetanus with triple antigen should have a card made out for them and given to their parents. Active immunization with tetanus toxoid also eliminates the annoying, and sometimes dangerous, allergic reactions to anti-tetanus serum."

I have had an encouraging response from some general practitioners, but it is necessary for them to receive payment for giving tetanus toxoid injections in the same way as they are paid for other immunizations. Only by doing so will the Ministry of Health ensure the banishment of this dread disease. I do not think casualty officers should be called upon to give the injections. Patients admitted to hospital after accidents should, however, have the first tetanus toxoid injection while in hospital or at a follow-up clinic.—I am, etc.,

Hull Royal Infirmary, Hull. J. G. ALEXANDER.

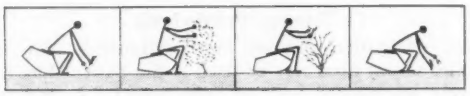
REFERENCE

[1] Douthwaite, A. H., *Materia Medica, Pharmacology and Therapeutics*, 31st edition, 1959. Churchill, London.

Backache and Gardeners

SIR,—In reply to Mr. W. H. Gervis (August 13, p. 541) I would readily agree with him that extension and hyperextension of the spine is a very important feature of "treatment." The apparatus that I described in my letter (July 23, p. 309) was designed especially to enable the gardener with backache to do many necessary jobs "with a straight back" and in comfort. It is not a form of treatment.

It has been proved successful in use by many gardeners. The sketches show several jobs that can be accomplished easily sitting down, but keeping the back straight and flexing the hips and knees.



Planting. Picking. Pruning. Weeding.

The height of the seat can be arranged for each individual by a cushion of foam rubber or plastic.—I am, etc.,

Kettering. FRANK RADCLIFFE.

SIR,—Mr. W. H. Gervis's letter (August 13, p. 541) is full of sound sense, but, like the back, it could, with advantage, be extended. We are formed with our eyes at the top and in front of us. As a result movements of flexion are much more numerous and strenuous than those of extension. Our hands work mostly in movements of flexions, very often sustained for long periods. This is accentuated in routine repetitive work. Not only our spines, cervical, thoracic, and lumbar, but our hands and feet are used in this one-sided manner. For the sake of accuracy of eye and hands we bend forwards and crouch downwards, because we prefer to work with the help of gravity. The remedy, as Mr. Gervis insists, is contrary extension.

Young people of both sexes should be advised of the benefit for the wear and tear of their spine of swimming with the back stroke. Stiff and painful hands are so mostly on the palmar flexor surface. Sesamoid bones are developed in the flexor tendons. Strenuous gripping with the hands, as in wringing clothes, can sometimes cause a subluxation of the lunate bone to the dorsal surface. In industry workers should be advised of a simple exercise of counter-extension which can be performed at any odd moment. If the fingers are interlaced each hand in turn can actively extend its own metacarpo-phalangeal joints while passively extending those of the other hand, and each can laterally move the other hand's first phalanges passively. Also the capsules of the metacarpo-phalangeal joints can be stretched by trapping and pulling the fingers of the other hand successively between the fingers and in the hand. Such simple self-treatment gives a feeling of freedom and relief from pain and discomfort.

Similar faults of habit at work occur in the feet. For the sake of a secure stationary position at work the metatarsal arch is pressed down and the toes become mere appendages cocked up against the roof of the shoes, where corns and callosities are formed. A woman, more than a man, when she is standing and intent upon a task tends to cock her toes up. This can be observed. In industry it is a good plan to hold a foot clinic at regular times in the week, at which the deformities of hallux valgus and the falling of the metatarsal arch can be explained and often corrected. Women should be advised to dance. A woman while dancing has often to walk backwards. For the sake of her own stability she tends to use the toes as part of her feet to support her and the toes will become part of the whole plantar arch, and the metatarsal arch will tend to rise.

Some of the worst cases of falling of the metatarsal arches I have encountered were in men driving a lorry with a heavy clutch. In such cases it is probably the anxieties of driving in traffic that cause a continual spasm in the left foot and toes. Passive correction of the deformity by the medical officer and his assistants, nurses, or physiotherapists, and instruction in the nature of the deformity and how to hold the feet correctly, will give great relief. Forced passive movements of ankle and mid-tarsal joints improve the feeling of well-being in the feet.—I am, etc.,

Buntingford, Herts. E. H. STRANGE.

Promazine Overdosage

SIR,—I have, I regret to say, read only to-day your issue of May 14 in which you print (p. 1507) an interesting letter from Drs. W. Hindle and D. Negus on the use of noradrenaline in unconsciousness due to an overdose of promazine.

Some years ago, when noradrenaline was new, I was assisted at one of my hospitals by a registrar and house-physician who had both retained their interest in physiology. One evening a woman was admitted in so deep a state of unconsciousness due to barbiturate poisoning that she was tantamount to a decerebrate animal. Her death appeared to be inevitable, and the young men seized their chance of testing on a human decerebrate animal the effects of certain drugs, one of which was noradrenaline, newly introduced. They set up a drip which raised her unmeasurable blood-pressure to a reasonable figure. After giving precise instructions to the night staff they retired to their well-earned rest. In the morning, when they visited the patient, they found that the night staff had disregarded their instructions and had kept the drip running through the night. They were unable to measure her diastolic pressure, which was higher than the maximum reading on the sphygmomanometer. The patient was feeling fine and

eating her breakfast. She never looked back. I have been unable to persuade any of their successors to repeat the experiment.—I am, etc.,

London, S.W.3. RAYMOND GREENE.

Fromm on Freud

SIR,—Despite his manful efforts to be fair, I do not think that John Cohen, in his review of Erich Fromm's *Sigmund Freud's Mission* (August 13, p. 514) succeeds in doing justice to an important book. Certainly his opinion that it " will be judged by posterity as little more than a footnote " to Ernest Jones's filial biography is wide of the mark. Fromm provides an alternative view from which Freud is seen as a human being, compact of strength and weakness, and not as a demigod. There is a closely reasoned and cogent argument, supported by biographical data and documented by quotations from Jones, Ferenczi, Sachs, and Freud's own letters. Future biographers will not be able to blink the facts adduced by Fromm, and will have to give radical consideration to his conclusions. The review also fails to bring out what a brilliantly written and fascinatingly readable book this is.—I am, etc.,

The National Hospital, London, W.C.1. ELIOT SLATER.

Health at Work

SIR,—Your advocacy (August 6, p. 445) of " the development of industrial health services " is very welcome. But need these services include the general nation-wide establishment of laboratories for this special purpose ? That we need some specialized reference laboratories to deal with the more unusual and less widespread problems, as we have in the bacteriological reference laboratories of the public health laboratory service, is probably true, but can we not graft most of the laboratory work on to existing group laboratories ? I am thinking particularly of the control of the health of individual workers in industries with hazards whose effects—for example, those of lead—fall within the scope of a well-equipped group laboratory. We ourselves give a moderate amount of such service, which could be economically stepped up by enlarging our establishment, to industrial concerns in our area. We find this particularly valuable when the factory medical officer is a general practitioner with whom we are already in close contact. The truth is the country cannot afford either the equipment or the technicians to set up a completely new chain of laboratories, but we could improve the scope and efficiency of many hospital laboratories by enlarging them to take on a good deal of what should be done for occupational health.—I am, etc.,

Pathological Laboratory, Kingston Hospital, Surrey. D. STARK MURRAY.

SIR,—Your thoughtful leading article on health at work (August 6, p. 445), has much to commend it and we do not wish to take issue with its general theme. However, the statement that the two great gaps in the industrial health services of this country to-day are the lack of special provision in small factories and the lack of industrial hygiene laboratories omits a third important category. The wisdom of caring for the worker's physical health is established beyond doubt ; but what of his mental health ?

Emotional illness probably causes more absenteeism than any other illness, except the common cold, and psychological factors perhaps outweigh all others in industrial sickness.[1 2] High priority should be given to the establishment of psychiatric programmes in industry. The dearth of trained psychiatrists must preclude any large-scale schemes, but the arguments for consultations in the factory between the industrial medical officers and psychiatrists are considerable. The lack of collaboration between existing mental health provisions and industrial medicine is deplorable, and attempts to bridge it have been negligible. The distrust of industry towards psychiatry and the fear that the specialist in this field may undermine working morale is certainly outdated.

In the United States several large industrial corporations have full- or part-time psychiatrists on their medical staff who are dealing successfully not only with psychological casualties but co-operate with the management and workers in the establishment of better interpersonal relations. The essence of such mental health programmes is the detection of the emotionally disturbed worker, before he gets into serious difficulties. Many cases could be helped at factory level while they stay at work. Current policies of the Ministry of Labour, the large foundations, and of doctors and executives in industry indicate that they are unaware of *mens sana in corpore sano* among workers. The most important point is to acknowledge that there is a mental health problem of considerable dimensions in industry, and then to do something about it before Great Britain once again lags behind in the leadership of the industrial world.—We are, etc.,

J. A. HARRINGTON.
W. MAYER-GROSS.

Birmingham, 13.

REFERENCES

[1] *Brit. med. J.*, 1953, **1**, 604.
[2] Markowe, M., *J. ment. Sci.*, 1953, **99**, 92.

Routine Haemoglobin Estimations

SIR,—May I congratulate your journal on the excellent summaries of the scientific sections at the annual meeting held at Torquay recently ? The 6,000 miles separating Johannesburg and Torquay were overcome by careful filtering of all the important features. Each section contained much of interest and much for discussion. One particular statement, under the General Practice Section on " Anaemia and Heart Disease " (July 2, p. 57), however, is wide open to correction. It reads, " The only certain method of diagnosis [of anaemia] was for the family doctor to carry out haemoglobin estimations himself, *but this was obviously not a practical procedure.* . . ." (My italics.)

Haemoglobin-estimating machines are readily obtainable, and one in particular, the American Optical Co. haemoglobinometer, seems to be the most accurate. The haemoglobin estimation, using the latter machine, can be performed in less than one minute. It merely consists in pricking the patient's finger, putting one drop of blood on the glass slide provided, and reading off the haemoglobin—the latter result being given in both grams % (from 13.8–15.5 as normal) and percentage. Thus even a busy practitioner can estimate the haemoglobin in less time than it takes to form a probably incorrect assessment of the colour of the conjunctivae, pallor of hands, and finger-nails. In any event, part of the physical examination should surely include the haemoglobin examination just as surely as it includes an examination of the urine. Only if this is done as a routine, as it should be, will the large numbers of cases of anaemia, especially in women, be detected.—I am, etc.,

Johannesburg. HERBERT KRAMER.

After-care Sisters in Accident Service

SIR,—The efficiency of an accident service depends entirely on the work of the accident team. Frequent changes of the junior medical and nursing staff militate against the efficient application and change of plasters, etc.

In the Windsor Group accident service, however, this has been overcome by the use of after-care sisters who are orthopaedic nursing sisters and have special training in plaster technique and the fitting of appliances. We have followed the pattern long established in certain orthopaedic hospitals such as Oswestry and Oxford, but have found it more convenient to have trained sisters doing this work instead of physiotherapists; but the principle is the same otherwise.

These after-care sisters are most valuable in the fracture clinics and during an emergency. They do all the work associated with plasters and appliances in the clinics. We believe they produce a higher standard of plaster work than can be obtained otherwise. This is particularly appreciated by the patients and the parents of young children. These sisters perform a valuable function in an accident service both on grounds of efficiency and economy, and their vocation is a satisfying one.

If establishments were provided for these sisters we believe there would be no shortage of applicants coming from the famous long-term orthopaedic hospitals in this country. But at the moment this system appears to be very limited in use and the advantages are not appreciated.—We are, etc.,

ROY MAUDSLEY.
G. P. ARDEN.

Windsor.

Phenothiazine Derivatives

SIR,—Dr. Linford Rees, in his article on this subject (August 13, p. 522), states, in the table on p. 523, that no toxic effects on bone marrow have so far been reported in relation to trifluopromazine ("vespral"). However, there is a description by Frank J. Ayd[1] of a case of fatal agranulocytosis due to this drug.—I am, etc.,

R. PAKENHAM-WALSH.

Lancaster Moor Hospital, Lancaster.

REFERENCE

[1] *Amer. J. Psychiat.*, 1958, **114**, 940.

Spontaneous Regression of Cancer

SIR,—Occasional cases of true spontaneous regression of malignant disease are reported in the medical press, though since 1900 rather more attention has been paid to this subject in America than in this country. Everson and Cole[1] reviewed 600 cases published or communicated to them between 1900 and 1956 and considered 47 of them sufficiently well documented to stand examination.

There are several types of regression but those of most immediate interest are (1) cases in which the primary and secondary tumours disappear for many years either with no treatment or following palliative measures; (2) cases in which secondary tumours disappear after removal of the primary.

In order to be acceptable such cases need (*a*) initial biopsy sections available which are unequivocally malignant; (*b*) either no treatment given or such treatment as in similar cases has proved ineffective; (*c*) several years' survival with clinical regression of the tumour; (*d*) subsequent surgery at the tumour site revealing no malignant disease; or (*e*) subsequent necropsy following death from non-malignant disease revealing no malignant condition remaining at the original site.

Most of the recorded cases are neuroblastomas, which mature to ganglioneuromas, carcinomas of bladder, and endocrine conditional tumours, which regress after natural menopause. In the cases so far collected and unpublished some are not in these well-recognized groups.

As it is felt that some useful knowledge might be obtained by reviewing a number of such cases, the South Metropolitan Cancer Registry is attempting a survey, and this is an appeal for information. General practitioners, surgeons, and radiologists seem the most likely people to encounter cases and I should be grateful for their co-operation. If details, however meagre, could be sent to the registry the documentation will be undertaken with as little trouble to the doctor and patients as possible. Any conditions of limitation that the doctor cares to impose will of course be strictly observed.—I am, etc.,

DOUGLAS NELSON.

South Metropolitan Cancer Registry, Clifton Avenue, Belmont, Sutton, Surrey.

REFERENCE

[1] Everson, T. C., and Cole, W. H., *Ann. Surg.*, 1956, **144**, 366.

Maternal Mortality

SIR,—You are to be congratulated on the substance of this leading article (July 9, p. 123). Perhaps, however, it would have been relevant to refer to the present inadequate obligatory number of ante- and post-natal attendances required and the unsatisfactory remuneration for this unborn minimum. Fellow general practitioners with whom I have discussed this topic feel with me that you have neglected a golden opportunity.—I am, etc.,

C. F. R. MALLETT.

Ipswich.

Safety Cap for Motorists

SIR,—A modest but useful contribution to the prevention of injuries on the road is a cap for men and a hat for women reinforced in such a way as to reduce the impact on the skull when a motorist or passenger is involved in an accident. The designs for this headgear were worked out by the British Hat and Allied Feltmakers Research Association (Stanley House, Fairfield, Manchester). Neither the cap nor the hat is inelegant and the manufacturers have been at some pains to make them acceptable to people who, even in matters of this kind, are particular about appearances.

In 1959 you published[1] an important letter from Mr. W. Gissane in which he gave a detailed description of the physical properties of the protective cap, and also pointed out that 65% of injuries to the occupants of motor-cars involve the head. The difficulty is to get these things, and in one case it was necessary to go direct to the wholesalers. There is now a great run—and a welcome one—on safety belts, but it appears that, owing to the lack of demand for the caps and hats, retailers are reluctant to stock them.

All doctors must feel deeply concerned about casualties on the road. If by example, as well as by precept, they could popularize this protective headgear the incidence of serious head injury among motorists might well be reduced. The way to start, I suggest, is to obtain caps

and hats for themselves and for members of their families. I have bought five.

One last point. As yet few cars have safety belts and you cannot take your own when travelling in a strange car. You can take your hat.—I am, etc.,

The Institute of Orthopaedics, London, W.1. H. J. SEDDON, President, British Orthopaedic Association.

REFERENCE

[1] Gissane, W., *Brit. med. J.*, 1959, **1**, 235.

Cat Phobia

SIR,—In your issue of August 13 (p. 497), writing of a case of cat phobia treated by them, Dr. H. L. Freeman and Mr. D. C. Kendrick are guilty of an inaccuracy sufficiently gross to merit correction on my part. In their brief and pejorative survey of the results of psychotherapy of mental disorders, they say, *inter alia*: "Glover (1955) has disavowed any claims for the therapeutic usefulness of psycho-analytic methods." I gather from their list of references that the disavowal was made in my textbook *The Technique of Psycho-analysis*. This is, I need hardly say, news to me, the more startling in that the book in question was devoted to instructing analytical students and practitioners how to carry out psycho-analytic treatment successfully.

I have, it is true, time and again emphasized that before embarking on treatment of mental disorders one should establish the suitability of the case; and I have constantly insisted on the necessity for a carefully controlled statistical appraisal of results based on reliable after-histories. But of course these recommendations do not apply to psycho-analysis alone; they are even more pertinent to other psychiatric or eclectic techniques, not excluding that form of "behaviour therapy" which disguises its psychological origins under neuro-physiological captions such as "reciprocal inhibition," or "conditioning" or "learning response modifications" or what not. I have also maintained that any form of therapy will secure its quota of satisfactory results; and in a critical analysis of Wolpe's *Psychotherapy by Reciprocal Inhibition* (to which our present authors refer) I have pointed out that the rationale of Wolpe's technique depends on the exploration (witting or unwitting) of both molecular and molar suggestion.[1]

But whatever the form of non-analytical treatment and whatever its symptomatic success, it has always seemed regrettable to me that the patient should be left with his or her mental conflicts intact, a state of affairs that is well illustrated by the case of cat phobia that Dr. Freeman and Mr. Kendrick now report.—I am, etc.,

London, W.1. EDWARD GLOVER.

REFERENCE

[1] Glover, E., *Brit. J. med. Psychol.*, 1959, **32**, 68.

POINTS FROM LETTERS

Diastolic Reading

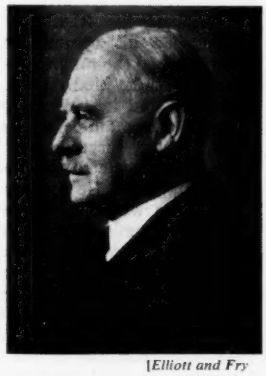
Dr. R. P. W. KUP (Gobowen, Salop) writes: During estimations of blood-pressures, using the ordinary sphygmomanometric method, I have frequently noticed positive signs of apprehension exhibited by the patient, and often even a physical "jump," transient but coincidental with the diastolic reading. When it occurs I now take this point as the diastolic reading with little regard to the fading sound in the stethoscope. I have never heard any description of this phenomenon, and it is interesting to speculate on the cause of it. Surely I am not the first to have noticed it?

Obituary

LORD HADEN-GUEST, *M.C.*, M.R.C.S., L.R.C.P.

Lord Haden-Guest, who was a medical officer to one of the earliest child-welfare clinics in London and then became a well-known Labour politician, died on August 20. He was 83 years of age.

Leslie Haden Guest was born at Oldham, Lancashire, on March 10, 1877, the son of Dr. Alexander Haden Guest, who practised in Manchester and had many friends among the Fabians and radical thinkers of his day. Educated at William Hulme's Grammar School and at Owens College, Manchester, Leslie Haden Guest continued his medical training at the London Hospital, qualifying M.R.C.S., L.R.C.P. in 1900. After serving as a civil surgeon in the South African war he remained in South Africa for a time and then returned to London, obtaining an appointment as assistant school medical officer under the London County Council. Working in Southwark, he founded, and became medical officer of, the St. George's Dispensary and School Clinic. Later he became chairman of the executive committee of the dispensary as well as consulting physician. Observations made at the dispensary gave impetus to the setting up of the school dental service of the L.C.C. His interest in the health and welfare of children was life-long, and he was for a time joint honorary secretary of the Save the Children Fund with the founder, the late Eglantyne Jebb.



[*Elliott and Fry*

On the outbreak of war in 1914 Haden Guest was appointed medical director of the hospital set up in the Hotel Majestic, Paris, under the French Red Cross. He was also a founder and organizer of the Anglo-French Committee of the British Red Cross Society and Order of St. John. Afterwards he joined the R.A.M.C., and was D.A.D.M.S., with the rank of major, with the 14th and 58th London Divisions, winning the Military Cross at Passchendaele in 1917 for rescuing wounded men under fire. In the following year he served in Egypt and Palestine.

After the war Haden Guest helped to organize relief work among the children of Vienna and Budapest, and set up hospitality committees for children from the famine-stricken areas. He acted as secretary and medical adviser to the Labour Party delegation to Russia in 1920, and three years later he contributed to this journal a lengthy article on public health in Soviet Russia. As a young man his enthusiasm for social reform was kindled by the people he met in his father's home, and while practising as a physician in Westminster and in the City he took an active interest in political and social affairs. He represented East Woolwich on the London County Council from 1919 to 1922. He then stood for Parliament at the General Election in November, 1922, as the Labour candidate for North Southwark, but failed to secure the seat. In December of the following year, however, he successfully contested the same constituency, again on behalf of the Labour Party, although his majority was only 362 in a total poll of 14,968. He was appointed Parliamentary Private Secretary to the Minister of Health in the first Labour Government in 1924, and in 1925 he was a member of the Empire Parliamentary delegation to Canada and Newfoundland. In March, 1927,

Haden Guest gave up his seat in the House of Commons on his retirement from the Labour Party, and he unsuccessfully stood for Parliament at the General Election in May, 1929, as the Conservative candidate for North Salford. Soon returning to the Labour Party, he stood as the Labour candidate for the Wycombe division of Buckinghamshire in October, 1931, and in November, 1935, as the Labour candidate for Brecon and Radnor, but was defeated at both elections. After a lapse of ten years he was again returned to Parliament in 1937 as Labour Member for North Islington. He successfully contested the same constituency at the 1945 General Election, relinquishing the seat in January, 1950, on his elevation to the peerage as Baron Haden-Guest, of Saling in the county of Essex.

Haden-Guest was a member of the commission which left London in October, 1938, for Lagos to report on the interrelationship between Government officials, traders, and natives in the West African colonies and on the general development of resources. In the second world war he again joined the R.A.M.C. as a lieutenant in 1940, but relinquished his commission in September, 1941, having again attained the rank of major. In 1945 he was appointed chairman of the Medical Priority Committee of the Ministry of Health and in 1952 chairman of the National Medical Manpower Committee. He resigned from the chair in 1955, when he was succeeded by Sir Zachary Cope. In 1946 he was a delegate to the Food and Agriculture Conference in Washington. He made a three months' tour of the Far East in the winter of 1946–7 as chairman of the Medical Priority Committee to make a study of districts where British Forces were stationed. He had previously visited the British Army of the Rhine in a similar capacity in 1945.

A founder of the Labour Party Commonwealth Group, Lord Haden-Guest was also a member of the Parliamentary Committee on the evacuation of the civil population in 1938, and chairman of the Medical Parliamentary Group. He succeeded Lord Boyd-Orr as president of the Association of Scientific Workers in 1950, and in February, 1951, was appointed a Lord-in-Waiting to the late King George VI, in succession to the late Lord Darwen, and for some years he was Assistant Opposition Whip in the House of Lords. He had been secretary of the Leverhulme Research Fellowship Committee since 1933, the year in which the fellowships were first offered. He was a member of the Central Medical War Committee from 1943 to 1951; of the Aliens Committee of the British Medical Association from 1943 to 1950; and of the B.M.A.'s Services Committee in 1951–2. He was also a member of the Medical Planning Commission in 1940. He wrote books and papers on numerous social and medical subjects, being the author of *The Nation of the Future* (1915), *The Care of Infants and Children* and *The Struggle for Power in Europe* (1921), and was editor, with Sir Harry Johnston, of *The Outline of the World of To-day* (1923).

Lord Haden-Guest married three times. By his first wife he had two sons, and by his second two sons and one daughter. In 1944 he married Edith E. Macqueen, who survives him. The heir to the barony is the elder son of his first marriage, the Hon. Stephen Guest.

Lord TAYLOR writes: Leslie Haden-Guest was not an easy man to get to know. He kept himself to himself, and even among his medico-political colleagues he never "let his hair down." He was more at home with a pen than with his tongue, and his weekly appreciations of Parliamentary doings in the *Lancet*, under the signature of Medicus M.P., showed a vivid and surprising insight and appreciation of public affairs. I remember Dr. Egbert Morland saying how his real breadth of experience was shown by the letters *M.C.*, M.R.C.S., M.P. after his name. Partly, I think, his reticence was due to his having left and then rejoined the Labour Party; he felt his colleagues minded, when in fact nothing was further from their thoughts. The people of North Islington, whom he represented in Parliament, remembered him for many years after he left them: "The doctor was a real gentleman," I often heard said. For some years he was part-time secretary of the Leverhulme Research Fellowship Committee; when he retired, he was not well off. The job he enjoyed most was his chairmanship of the Medical Personnel Priority Committee during the war; this, he felt, was really useful work. In 1951 he was a Government whip in the Lords. His later years were marred by increasing ill-health.

Haden-Guest gave up his life to a political career, and sacrificed much in doing so. He lived to see the achievement of much of what he stood for. He was not of the stuff that first-rank politicians are made of; but his quiet contributions to the world of medicine and politics were of greater value than those of many who flash more brightly.

WILLIAM BLACKWOOD, D.S.O., M.B.E.

M.B. Ch.B.

Dr. William Blackwood, who practised for many years at Camborne, Cornwall, died on July 31 at the age of 82.

William Blackwood was born on April 12, 1878, the son of Mr. A. Blackwood, of Moffat. Educated at Lincoln School and the University of Edinburgh, he graduated M.B., Ch.B. in 1902. Shortly after qualification he went to Camborne, where he practised uninterruptedly until 1958, with the exception of four years' Army service during the first world war.

E. T. writes: The death of William Blackwood has taken a long familiar and much loved figure from the life of West Penwith. His half century of medical practice was only the least of his many achievements, for he lived a full and strenuous life, holding many appointments and taking an active part in the life of the community of West Cornwall. His distinguished war service was typical of his energetic and practical approach to the problems of his time. Taking with him many Camborne men in the 2/1 Wessex Field Ambulance, he became Lieutenant-Colonel, R.A.M.C., received the D.S.O. and bar for his courage and devotion to duty in maintaining advanced dressing stations in contact with the enemy, and was three times mentioned in dispatches. He never forgot the comradeship of those days, for he founded, and until his retirement in 1958 was chairman of, Camborne Old Comrades Association. During the second world war Dr. Blackwood was chairman, in Cornwall, of the Joint Red Cross and St. John War Organization, medical adviser to the Home Guard, and commandant for first-aid of Cornwall's war-time A.R.P. service, and was awarded the M.B.E. for his services.

Dearest perhaps to his own heart was his work with the St. John Ambulance Association, which he served devotedly for over 50 years. Early in his life in Cornwall, horrified by the lack of facilities for dealing with injured tin miners, he founded the Camborne St. John Ambulance Division and was its first honorary surgeon. From then on he devoted an immense amount of time and work to the teaching of first aid, and it was largely through his efforts that an adequate system of first aid was established in the then flourishing tin mines of the district. He was county ambulance commissioner from 1932 to 1950, and recognition of his services came in his promotion to Knight of Grace of the Order of St. John.

For many years he was chairman of the National Service medical board, and his work as police surgeon, factory medical officer, Treasury medical officer, and medical referee to the Ministry of Labour brought him influence and authority even greater than accrued through his large and widespread general practice. In the early years of this century there were very limited medical facilities and virtually no consultants or specialists in Cornwall, so that a country doctor had to accept full responsibility for everything from broken limbs to obstructed labour, from appendicitis to typhoid fever, and that without benefit of easy transport and an effective therapeutic armamentarium. One remembers the old farmer relating how he had typhoid in his youth and was visited twice a day for two months by Dr. Blackwood, who bicycled nightly each way the ten miles that separated his farm from Camborne. More often than not operations were performed on the kitchen table in the patient's own

home, though for many years Dr. Blackwood was an honorary surgeon on the staff of Redruth, Helston, and St. Ives Cottage Hospitals and operated in all of them in addition to his heavy practice duties. He excelled in domiciliary midwifery, and his extensive obstetric practice was the foundation of his highly successful general practice. To watch the dexterity, speed, and skill with which he applied forceps was both a privilege and an education.

But it was as a family doctor that he would wish to be remembered, and few could lay better claim to that title. He was a strikingly handsome figure, much beloved by his wide circle of patients and friends in West Cornwall, who will long remember with gratitude his kindliness, his sympathetic understanding, and his unfailing help and practical advice. An old patient once pointed out to a new partner four photographs on his sitting-room wall with the explanation, "Those are my grandfather, my father, myself, and my son, and Dr. Blackwood attended us all, for he saw my grandfather out of the world and both my son and me into it." To have served four generations of a community is an opportunity given to few men, but William Blackwood did more than that, for by his devotion to his patients and his personal example he helped to establish a standard of family medical care in West Cornwall which will survive as his true memorial.

He is survived by his widow, daughter, and two sons, both of whom carry on the family medical tradition.

D. D. PAYNE, M.D., D.P.H.

Dr. D. D. Payne, medical officer of health of the Borough of Harrogate and divisional medical officer in the West Riding of Yorkshire, died suddenly on August 5 while on holiday in Oxford. He was 57 years of age.

Donald Derry Payne was born in Upper Norwood on May 13, 1903, and received his early education at Dulwich College and Eastbourne College, and his medical education at St. Thomas's Hospital, where he qualified in 1930. After holding a number of clinical assistantships at St. Thomas's Hospital he became casualty officer at the Royal Waterloo Hospital and house-surgeon at the Westminster Hospital. In 1932 he graduated M.B., B.S., proceeding M.D. two years later. He had always intended to make his career in public health, and, having gained, in open competition, a studentship at the London School of Hygiene and Tropical Medicine, he obtained the D.P.H. in 1934. Later he worked as a medical officer at a London County Council fever hospital and in 1935 he was appointed assistant medical officer of health at Tunbridge Wells. Two years later he became deputy medical officer of health at Croydon, where he rendered valuable service during a typhoid epidemic.

In 1940 Dr. Payne was appointed medical officer of health at Harrogate, and in 1947 he received the additional appointment of divisional medical officer under the West Riding County Council, and he was also M.O.H. of Knaresborough and Nidderdale.

An active member of the British Medical Association, he was one of the joint honorary secretaries of the Harrogate Division from 1940 to 1950 and chairman of the Division in 1951–2. He was a vice-president of the Section of Preventive Medicine at the Annual Meeting in Harrogate in 1949, and former president of the Yorkshire Branch of the Society of Medical Officers of Health.

Dr. Donald Payne and his wife were both well known for the active support they gave to many local causes, including particularly the Boy Scouts and Girl Guides, and he will be greatly missed.

N. V. H. writes: The sudden death of Donald Derry Payne removes a well-loved personality from Harrogate and district. An able administrator in his chosen specialty of public health, he built up a department during his twenty years in Harrogate which was an object of admiration to his colleagues. This was largely the result of the personal interest he took in every member of his staff and their work. Payne was a man with an unbounded capacity for friendliness and one always found that meeting him on official business was a pleasant experience.

His interests were wide. He took an intense interest in the Scout movement, which he served with distinction for many years, having been County Commissioner for the Central Yorkshire Area since 1956. An enthusiastic Rotarian, he was a member of the Harrogate Club, of which he was president in 1950–1.

Payne's humanity illuminated all his dealings, official and otherwise, and a multitude of friends in all walks of life mourn the passing of a very efficient, practical, and lovable Christian.

Vital Statistics

Poliomyelitis Vaccination

The number of children under 15 in Great Britain vaccinated against poliomyelitis at the end of June, 1960, was over 10 million, and the total of all vaccinated persons had nearly reached 14½ million, over 10½ million of whom had received three doses of vaccine. The acceptance rate for children is now 77%, and the average monthly number of injections during the second quarter of the year was 1.1 million.

A recent circular (E.C.N. 337) from the Ministry of Health reviews the latest information about the relation of poliomyelitis vaccination to other immunizing procedures (revising circular E.C.N. 218). As a general rule at least two weeks should elapse after vaccination against poliomyelitis before any other immunizing procedure is undertaken. When immunization with a toxoid or killed vaccine has been performed the minimum interval before vaccination against poliomyelitis should also be two weeks; when a live vaccine has been used—that is, against smallpox or yellow fever—an interval of at least three weeks is desirable. So far as B.C.G. vaccination is concerned, at least four weeks should elapse between poliomyelitis vaccination and the complete B.C.G. programme, whichever is performed first. While the choice of order will be governed by individual circumstances, it will usually be more expeditious to vaccinate against poliomyelitis before undertaking B.C.G. vaccination.

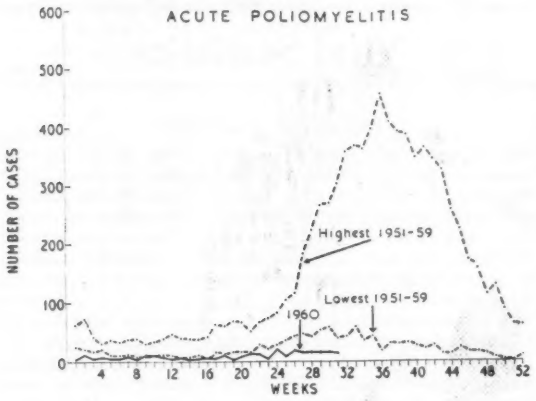
Infectious Diseases

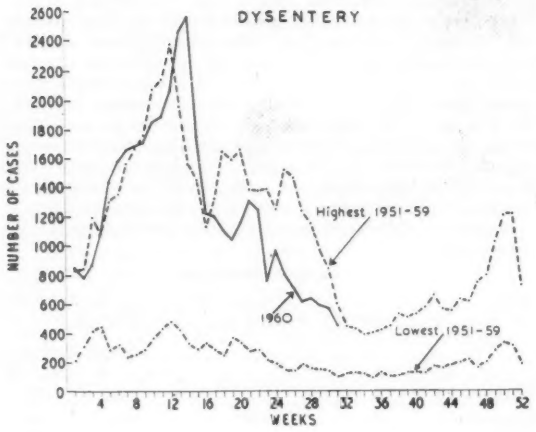
Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

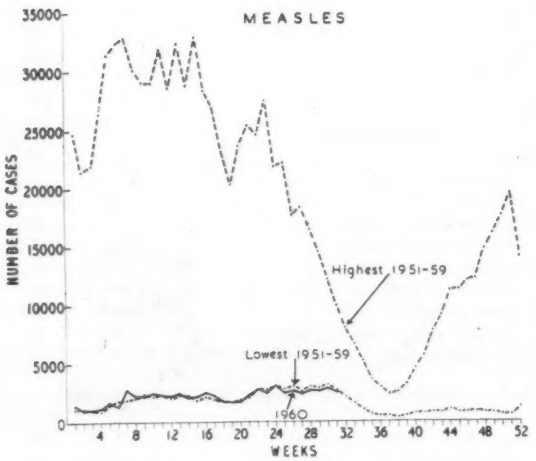
	Week Ending Aug. 6	Week Ending **Aug. 13**
Dysentery		
Cheshire	8	**21**
Lancashire	69	**64**
Liverpool C.B.	18	**11**
London	54	**64**
Lewisham	4	**19**
Yorkshire West Riding	73	**44**
Leeds C.B.	17	**12**
Glasgow	59	**141**
Food Poisoning		
Sussex	16	**18**
Eastbourne C.B.	12	**0**
Horsham U.D.	0	**13**
Soke of Peterborough	0	**20**
Peterborough M.B.	0	**20**
Lancashire	38	**36**
Liverpool C.B.	26	**21**
Glamorganshire	26	**19**
Cardiff C.B.	0	**14**
Cowbridge R.D.	32	**0**
Measles		
Lancashire	782	**683**
Liverpool C.B.	208	**180**
Manchester C.B.	96	**97**

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **August 6** (No. 31) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	2	0	0	0		2	0	2	4	
Dysentery ..	448	54	109	11		365	27	161	13	3
Encephalitis, acute	2	0	0	0		0	0		0	
Enteric fever:										
Typhoid ..	2	0	1	0		3	0	0	1	
Paratyphoid ..	7	3	0	0		3	0	2(B)	2	1(B)
Food-poisoning ..	236	26	128	2		250	34	20	3	
Infective enteritis or diarrhoea under 2 years				21					12	23
Measles*	2,545	147	35	0		4,598	117	65	99	51
Meningococcal infection	12	1	16	1		17	3	13	2	1
Ophthalmia neonatorum	18	3	2	0		27	2	11	0	
Pneumonia† ..	135	7	74	1		130	8	80	3	
Poliomyelitis, acute:										
Paralytic ..	4	1	0	} 0		{ 23	5	0	} 0	2
Non-paralytic ..	10	2	1			{ 17	0	3		
Puerperal fever§ ..	145	18	6	0		182	40	7	2	
Scarlet fever ..	316	19	30	9		463	24	43	11	9
Tuberculosis:										
Respiratory ..	351	39	49	9		353	27	56	11	
Non-respiratory	45	7	11	1		53	6	10	3	
Whooping-cough	1,193	141	112	3		614	32	99	14	64

DEATHS	1960					1959				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		1	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	2	1	1	0	0	6	0	1	0	0
Influenza	1	0	0	0	0	5	1	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	1				0	0		
Pneumonia ..	327	18	17	15	5	298	23	5		7
Poliomyelitis, acute	0	0		0	0	3	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 60	{ 4	5	0	1	} 42	{ 4	5	0	2
Non-respiratory		{ 0	1	0	0		{ 0	3	0	0
Whooping-cough	0	0	1	0	0	0	0	0	0	0
Deaths 0–1 year ..	290	32	29	6	9	266	21	28	5	4
Deaths (excluding stillbirths) ..	8,124	642	510	96	113	7,462	569	483	96	118
LIVE BIRTHS ..	14,085	1192	1070	229	358	13,430	1134	1044	229	357
STILLBIRTHS ..	280	17	31			293	21	21		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Rockefeller Foundation Grants

In the second quarter of this year the Rockefeller Foundation made grants totalling $8,263,908, of which $3,949,058 went to the medical and natural sciences.

This sum included $1½m. to the Harvard Medical Center for a central medical library that will serve the Center and the medical schools of Boston University and Tufts University; $500,000 to the All-India Institute of Medical Sciences, New Delhi, towards building and equipping a teaching hospital; $288,000 to the University College of the West Indies Faculty of Medicine for research and training; $230,000 to the American University of Beirut, Lebanon, to improve its facilities for training medical teachers and research workers; and £50,000 over three years to the Ministry of Health, Nairobi, Kenya, to establish an instruction centre for training health workers for village medical centres.

Western Provident Association for Hospital and Nursing-home Services

In its *Tenth Annual Report for 1959* the Western Provident Association for Hospital and Nursing-home Services, a mutual, non-profit-making organization operating throughout Great Britain and Northern Ireland, draws special attention, firstly to its substantial reserves—investments costing £90,168 with an additional market value at the end of 1959 of £64,703, and, secondly, to its group terms (for at least six subscribers) which represent a discount of about 33⅓% on individual subscription rates. A special scheme for members of the medical profession has recently been started, and group terms are available to all registered medical practitioners willing to pay subscriptions annually in advance by bankers' order, as well as to those in a group of six subscribing *en bloc* through a hospital or professional association. A copy of the handbook describing the scheme in full will be sent on request to the head office of the W.P.A. at Royal London Buildings, 42, Baldwin Street, Bristol; very briefly, it covers grants towards the cost of treatment in hospital private wards and registered nursing-homes, medical fees, consultations, home nursing, etc., and supplementary cash benefits up to £10 10s. a week, all proportionate to the particular subscription rate that has been chosen. There is a special scheme for consultant colleagues' services, as some doctors may not feel the need for such extensive cover in this respect as the general public.

Professional Classes Aid Council

During the year, says the *Thirty-ninth Annual Report*, ending March 31, 1960, of the Professional Classes Aid Council, donations and subscriptions have amounted to £9,697.

Long-term grants were made to 423 families out of 807 applications—46 more than the previous year; £15,233 was distributed to them and an additional £3,508 on behalf of other charities. Temporary help accounted for £6,097; educational grants for £4,140; and training grants for £1,106. The Council hopes to move to new premises in the autumn, for which they will have to find £5,000 from capital. The President of the Council is Lord MORAN, P.P.R.C.P., and Sir ROBERT PLATT, P.R.C.P., is one of the Council's Patrons. The Royal College of Physicians, the Royal Medical Benevolent Fund, and the British Medical Association are represented on the Council.

Bristol Hospitals Fund

The *Twenty-first Annual Report of the Bristol Hospitals Fund* shows an increase of £1,196 in contributions last year. The general reserve was increased by a further £4,000. The Fund holds investments at cost of £53,330, and of a market value of £76,530 on December 31 last year. The claims paid were, at £36,233, £2,378 more than in 1958; 11,091 claims were settled during the year, an increase of 439. (Bristol Hospitals Fund (Inc.), Royal London Building, 42, Baldwin Street, Bristol, 1.)

Civil Defence Course for G.P.s

A civil defence course for general practitioners was recently arranged by the Ministry of Health at the Civil Defence Staff College, Sunningdale; it was attended by about 120 doctors, including 70 general practitioners nominated to attend by the B.M.A.

The first day included talks by the late Sir ERNEST ROCK CARLING (who was medical consultant to the Home Office), Professor J. E. ROBERTS (professor of physics as applied to medicine, the Middlesex Hospital), Dr. J. F. LOUTIT (director, M.R.C. Radiobiological Unit, Harwell), Professor B. W. WINDEYER (professor of radiotherapy, University of London), and Major-General F. R. G. MATTHEWS (commandant, Civil Defence Staff College). On the second day there was instruction in the organization of civil defence, the pattern of casualties, and the organization for dealing with casualties. It is hoped that further courses on the subject will be arranged on a regional basis.

Work Study in Hospitals

The Minister of Health has approved the appointment of additional officers for organization and methods and work study in the hospital service. They will take 12-week training courses, together with one-week appreciation courses in work study, at the Hospital Administration Staff College in the late autumn (see *Journal*, July 23, p. 323). Full details of the courses are not yet available, but provisional bookings may be made by application to the Principal of the Staff College, 2, Palace Court, Bayswater, London, W.2.

The work study team will be headed by Mr. P. J. TORRIE, at present head of the training section of the central work study department of Imperial Chemical Industries Ltd., while Mr. G. WESTON, group secretary of the Reading and District Hospital Management Committee, will be associated with the scheme on a part-time basis. Mr. K. OSBORNE, at present training and personnel manager of the Corner House Organization of J. Lyons and Co. Ltd., will join the staff to meet the expansion of the Staff College's general work.

Horder Centres for Arthritics

The MARCHIONESS OF DUFFERIN AND AVA, who is appeals chairman to the Horder Centres for Arthritics and who has privately bought a 54-acre site near Crowborough, Sussex, is granting facilities for the building of the first group of Horder residential centres upon part of this land. These will include both long- and short-term accommodation for the severely disabled, and treatment will be provided for both groups of patients. Inquiries to the Medical Adviser, the Horder Centres for Arthritics, 17, Rugby Mansions, Bishop King's Road, London, W.14.

Nechells Green Health Centre, Birmingham

Nechells Green Health Centre, the first in Birmingham, was opened by the then Minister of Health, Mr. D. WALKER-SMITH, earlier this year.

The centre, used by seven doctors, is built under a seven-story block of flats and houses, on its ground floor a suite of waiting-

[*Birmingham Corporation*

The Reception Hall, Nechells Green Health Centre.

rooms, surgeries, examination rooms, and offices. The welfare section includes facilities for antenatal care, mothercraft, relaxation, and sewing classes, with a children's welfare clinic, which has its own dental surgeries and recovery room. Offices have been provided for a home help organizer, and a district midwife and pupil have a flat above the centre. A resident caretaker ensures that messages reach the various doctors after surgery hours. Administrative work is dealt with by the reception officers, who receive phone calls and make hospital appointments as well as keeping the medical records. The centre costs £12,836 a year to run. (*Birmingham Post*, May 14.)

Committee on Preparation for Parenthood

As a result of recommendations made at the Conference on Human Relationships in the Care of Mother and Baby held in March, the Council of the Royal College of Midwives has set up an Advisory Committee to consider the need for research into (1) such teaching as is available for parents during the antenatal and post-natal periods in preparation for parenthood, and (2) whether the present teaching meets the needs of parents. The Committee includes Dr. HARVEY FLACK, Dr. DAVID MORRIS, and Professor NORMAN MORRIS.

Society of Apothecaries of London

The following have been elected officers of the Society for the ensuing year: *Master*, Dr. C. F. WHITE; *Senior Warden*, Mr. A. M. A. MOORE; *Junior Warden*, Mr. T. KEITH LYLE.

Family Doctor

The September issue of *Family Doctor* is now available, price 1s. 6d. It includes articles on "The Child Who Dreads School," by Dr. F. R. C. CASSON; "Learning to Read," by Sir CYRIL BURT; "On being Left-handed," by Dr. ANN MULLINS; and "The Facts about Disseminated Sclerosis," by Dr. J. N. WALTON.

Grants, Gifts, and Bequests

Birmingham University Medical School has acquired a particularly fine copy of the *De Humani Corporis Fabrica* (1543) of Andreas Vesalius. It is the last personal gift of the late Mr. FRANK BARNES, who wished to express in this way his satisfaction at the completion of the new Barnes library to which he and the late Dr. STANLEY BARNES had given so generously.

The late Dr. ANDREW BURY, of Cheshire, has left a third of the residue of his estate to Edinburgh University to found an annual prize for the best undergraduate male student of the year in pathology—with the proviso that the student must satisfy the dean of the medical faculty that he is Lancashire born and of the Protestant faith.

COMING EVENTS

B.B.C. T.V.—"They Made History": JOSEPH LISTER. Reconstruction of operation on broken knee-cap, September 1, 9 p.m.

College of General Practitioners.—Lecture, illustrated by colour photographs, on "Family Life and Family Practice in the U.S.S.R.," by Dr. JOHN H. HUNT, September 16, 8.30 p.m., at the Royal Society of Medicine, 1, Wimpole Street, London, W.1, for members and associates of the college and their friends. Admission by ticket only from the Secretary, 41, Cadogan Gardens, London, S.W.3.

"The Biology of Space Travel."—Symposium, September 29, 30, Lecture Hall, Royal Geographical Society, Kensington Gate, London, S.W.7. Details from the Institute of Biology, 41, Queen's Gate, London, S.W.7. (KNI 7339, 7412.)

Symposium: "Drugs for the Treatment of Hypertension."—Joint meeting, Royal Institute of Chemistry (Manchester and District Section) and Society of Chemical Industry (Manchester Section and Fine Chemicals Group), September 30, 2 p.m., Tenants Hall, I.C.I. (Pharmaceuticals Division), Alderley Park, near Macclesfield, Cheshire. Tour and dinner. Details from Dr. G. A. GAMLEN, Research Department, I.C.I. Ltd., Dyestuffs Division, Hexagon House, Blackley, Manchester, 9.

British Association of Physical Medicine.—Provincial autumn meeting, Royal Sussex County Hospital, Brighton, October 8. Details from the British Association of Physical Medicine, 47, Lincoln's Inn Fields, London, W.C.2. Acceptances by September 24.

British Diabetic Association (Medical and Scientific Section).—October 14: colloquium—at which obstetricians and paediatricians particularly welcome— on "Prediabetes," 9.50 a.m., Royal Faculty of Physicians and Surgeons, Glasgow. October 15: original papers on aspects of diabetes in general, 9.30 a.m. Registration fee for non-members, 5s. Details from Local Organizing Secretary, Dr. M. J. RIDDELL, Victoria Infirmary, Langside, Glasgow.

Joseph Strickland Goodall Memorial Lecture.—(Administered by Society of Apothecaries of London) Mr. T. HOLMES SELLORS: "The Evolution of Intracardiac Surgery," October 19, 5.30 p.m., Apothecaries Hall, Black Friars Lane, Queen Victoria Street, London, E.C.4. Open to members of the medical profession and senior students. Tea, 5 p.m.

Association of Military Surgeons.—67th annual convention, Mayflower Hotel, Washington, D.C., October 31, November 1, 2. Papers will include "Evaluation and Uses of Psycho-pharmacological Drugs." Details from the Association of Military Surgeons, 1726, Eye Street, N.W., Washington, 6, D.C., U.S.A.

American Thoracic Society (Medical Section of National Tuberculosis Association).—Annual meeting, Cincinnati, Ohio, May 22–4, 1961. Abstracts sought, by January 7, 1961, of papers on scientific aspects of tuberculosis and non-tuberculous respiratory diseases. Rules governing submission of abstracts from Mr. L. H. SCHMIDT, Ph.D., American Thoracic Society, 1790, Broadway, New York, 19, N.Y., U.S.A.

10th National Paediatric Congress.—Association of Spanish Paediatricians, Madrid, October 24–27. Sections on pathology of the newborn, tumours in children, and children's hospitals. Details from Dr. A. C. SANTILLANA, 17, Plaza de España, Madrid, 13, Spain.

NEW ISSUES

MEDICAL AND BIOLOGICAL ILLUSTRATION

Frontispiece.
Cerebellar Tuberculoma. Derek Martin.
Making Science Visible. Geoffrey Lapage.
Modern Binocular Indirect Ophthalmoscopy. William J. Stenstrom.
The Camera in Forensic Pathology. Keith Simpson.
The Predatory and Display Strikes of the Praying Mantis. K. D. Roeder.
Kineradiography with Image Intensifier and Television. R. Janker.
Billy Goes to Hospital. Sylvia Treadgold.
Equipment and Methods.
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Volume 10, No. 3. (Quarterly; £3 annually.)

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Young.—On July 27, 1960, at Cambridge, to Sylvia, wife of Oliver Young, M.B., a son.

DEATHS

Davies.—On July 23, 1960, Albert William Abell Davies, M.R.C.S., L.R.C.P., of Maesbury, 5, West Hill, Sanderstead, Surrey.
Drabble.—On July 22, 1960, Edward Percy Drabble, M.R.C.S., L.R.C.P., of Francis Dene, Penkridge, Staffs, late of Bloxwich, Staffs, aged 82.
Howard.—On July 18, 1960, at 2, Piersfield Close, Reigate Road, Ewell, Surrey, Daniel Clement Howard, L.R.C.P.&S.Ed., L.R.F.P.S., F.F.A. R.C.S., late of Edinburgh.
Inglis.—On July 24, 1960, at 1, Holehouse Road, Kilmarnock, Ayrshire, Edith Marion Douglas Inglis (formerly Smith), M.B., Ch.B., D.O.
Murray.—On July 26 1960, at his home, Littlehampton, Sussex, Andrew John Murray, *M.C.*, M.B., Ch.B., D.M.R.E., D.T.M.&H.
Shuttleworth.—On July 16, 1960, at West Dulwich Nursing Home, London, S.E., Walter George Adolphus Shuttleworth, M.B., B.Ch., late of Dulwich Village, London, S.E., aged 69.
Skae.—On July 11, 1960, in hospital, Harold Traill Skae, M.D.
Tallerman.—On July 25, 1960, Alice Campbell Tallerman (formerly Rose), M.B., M.R.C.P., D.A., of Woodlands, Sheering, Essex.
White.—On July 14, 1960, at his home, Newcastle Park, Galway, Thomas Kyran White, M.B., B.Ch., Colonel, I.M.S., retired.
Williams.—On July 10, 1960, Jack Islwyn Williams, M.R.C.S., L.R.C.P., of The Yews, Warmley, Bristol.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Bacterial Vaccines in Asthma

Q.—*Has any work been done on the value of catarrh vaccines in the prevention of colds in asthmatic children? What are the dangers, if any, of the use of such vaccines in these children?*

A.—The use of bacterial vaccines in the treatment of asthma was first advocated in the years 1914–17 by Charles Walker, of Boston,[1] and has been the subject of innumerable papers since. A wide variety of views have been expressed on their value; on the relative advantages of stock or autogenous vaccines; on the value of skin-testing with bacterial vaccines in selecting patients for treatment; and whether their action is specific or non-specific.

Frankland, Hughes, and Gorril,[2] of St. Mary's Hospital, in a controlled trial with some 200 patients of all ages with intrinsic (infective) asthma, found that autogenous bacterial vaccines produced no greater benefit than similar injections of carbol saline. In both groups over 50% of the patients benefited from the treatment.

From Rochester, U.S.A., Johnstone,[3] in a controlled study of the value of bacterial vaccines (stock in some cases and autogenous in others) in a total of 118 infants and children subject to repeated episodes of asthma associated with respiratory infections, found no significant difference between those treated with vaccines and those not so treated, nor did the type of vaccine used influence the degree of improvement. Exacerbation of symptoms has been recorded after an injection of vaccine, but with stock vaccines such reactions are most unusual.

REFERENCES
1 Hansel, F. K., *Clinical Allergy*, 1953, p. 761. London.
2 Frankland, A. W., and Gorril, R. H., *Brit. med. J.*, 1955, **2**, 941.
3 Johnstone, D. E., *Pediatrics*, 1959, **24**, 427.

Bananas in Diabetes

Q.—*Can bananas be used in a diabetic diet?*

A.—Bananas can certainly be taken by a diabetic as a ready source of carbohydrate. They should, however, be eaten ripe or preferably over-ripe, when they contain a mixture of sucrose, fructose, and glucose. In the unripe state they are composed largely of starch, which is poorly absorbed. An average banana contains about 10–15 g. carbohydrate and is also rich in minerals and vitamin C.

"Medical" Abortion

Q.—*What "medical" (i.e., non-surgical) methods of terminating pregnancy are safe and effective in the first three months?*

A.—Unfortunately—or fortunately—there are none.

Spacing of Immunizations

Q.—*How should vaccinations against yellow fever, poliomyelitis, and smallpox be spaced, and why?*

A.—On general principles it is reasonable and convenient, when time permits, to separate yellow-fever, poliomyelitis, and smallpox vaccinations, perhaps by intervals of four weeks; the intervals, however, may be shortened, as shown in the following schedule, without running any enhanced risk of reactions or of immunological interference between antigens. (1) Polio vaccine, first dose. (Interval: 2 weeks.) (2) Yellow-fever vaccine. (Interval: 4 days.) (3) Smallpox vaccine. (Interval: 3 weeks.) (4) Polio vaccine, second dose. (Interval: 6–12 months.) (5) Polio vaccine, third dose.

If the subject has had a previous successful vaccination against smallpox, the revaccination may be done at the same time as the yellow-fever vaccination. When primary smallpox vaccination is done before yellow-fever vaccination, some authorities suggest that three weeks should separate these procedures, but others believe that this is unnecessary. After smallpox vaccination (unless it is a revaccination) an interval of three weeks before any other preventive inoculation would reduce the likelihood of untoward effects that might be ascribed to, or aggravated by, the giving of various prophylactics at the same session.

The above schedule should not be used for infants under 7 months of age because of the possibility of maternally transmitted antibodies interfering with the response to the polio vaccine. For the younger baby the order of the inoculations may be altered so that smallpox vaccination is performed first—in the early weeks or months of life.

One of the recommendations of the Wellcome Symposium on Immunization in Childhood[1] was that smallpox vaccination should be carried out "some time during the first five years." Two doses of polio vaccine could then be given at the seventh and eighth month, the third dose being given 6–12 months later. Yellow-fever vaccine could then be given at the ninth month. Some authorities feel that, because of the remote possibility of an encephalitic reaction, infants should not be given yellow-fever vaccine before the age of 9–12 months.

REFERENCE
1 See *Brit. med. J.*, 1959, **1**, 1342.

Hard Water and Renal Calculi

Q.—*Is there any evidence which shows a relation between the prevalence of nephrolithiasis and hard-water areas in this country?*

A.—It is often asserted that nephrolithiasis is more common in hard-water areas in this country, but there is no scientific proof that this is so, and the majority of research workers interested in this problem are very sceptical about any causal relationship. On the other hand, a patient who already has a stone diathesis might be expected to grow stones more rapidly in a hard-water area, but even this is not proved.

Hazards of Transparentizing

Q.—*A method of preparing documents for photocopying is said to involve wiping them over with a solution consisting of trichlorethylene, B.P., 2 parts; tricresyl phosphate 1 part; and acetone, B.P.C., 1/8 part. An alternative method is to use a mixture composed of equal parts of carbon tetrachloride and castor oil. What risks might there be to clerical staff who operate this process?*

A.—Recently attention has been drawn to the fact that certain chemicals which may be used in the preparation of documents for photocopying are toxic substances, and that office workers who may have to handle them may be unaware of the hazards involved.[1] The chemicals concerned are trichlorethylene, tricresyl phosphate, and carbon tetrachloride. These substances are well known in industry as toxic chemicals, and they are dangerous in that they may be absorbed accidentally while being used in the normal way. All three are volatile, and can be absorbed in considerable quantities by inhalation.

Trichlorethylene is best known to the medical profession as a general anaesthetic, but it has many important industrial uses. When small amounts of the drug are inhaled it produces a pleasant sensation similar to the effects of mild alcoholic intoxication. Those who use trichlorethylene may become aware of this, and instances of habituation and addiction have been reported. Apart from this the repeated inhalation of trichlorethylene over a long period may have toxic effects on the nervous system and possibly the liver. It is also a substance which may cause contact dermatitis.

Industrial tricresyl phosphate consists of a mixture of three isomerides, *ortho-*, *meta-*, and *para*-tricresyl phosphate.

Of these the toxic effects of triorthocresyl phosphate are best known. If ingested it causes peripheral neuritis, and it is the substance responsible for the recent tragic outbreak in Morocco.[2] Cases of poisoning due to inhalation have also been reported,[3] and it is believed that sufficient triorthocresyl phosphate can be absorbed through human skin to constitute a real hazard in processes in which this compound is used repeatedly.[4]

Carbon tetrachloride is probably the best known of the three substances as an industrial poison. The dangers of inhalation are less well recognized than those of ingestion. A concentration of 1 part of carbon tetrachloride in 1,000 parts of air is said to be the upper limit of safety, and this may easily be exceeded if solutions containing carbon tetrachloride are in frequent use in a poorly ventilated room. Small doses may give rise to drowsiness, headache, nausea, and vomiting, and chronic poisoning may result in acute nephritis, toxic hepatitis, jaundice, and aplastic anaemia. Straus[5] reported three fatal cases of aplastic anaemia occurring in patients whose work had involved the use of carbon tetrachloride as a cleaning fluid in premises with poor ventilation, and the writer has recently seen a case of acute renal failure, fortunately not fatal, which followed the inhalation of fumes of carbon tetrachloride when a bottle containing cleaning fluid broke in a small ship's cabin.

This will give some idea of the possible dangers which may arise as a result of the use of these substances. Fortunately, although photocopying is now a common procedure, it is in only special circumstances that the process which may involve the use of these chemicals is required. This is the process of "transparentizing," in which a solution is applied to a document which has become opaque through age or handling so that it has to be made more transparent before copying. Although these toxic agents may be used in transparentizing fluids their use for this purpose is apparently uncommon.[6] It is obvious that if they are to be used then the strictest precautions should be taken. The premises should be adequately ventilated, the solutions used should be clearly labelled and marked "poison," and the personnel employed on the work should be fully aware of the hazards involved. Provided this is done the risks are not any greater than those run in many modern industrial processes which involve the use of such potentially toxic chemical agents.

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4 Hodge, H. C., and Sterner, J. H., *J. Pharmacol. exp. Ther.*, 1943, **79**, 225.
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Intervals between Polio Injections

Q.—*What is the maximum recommended interval between the first and the second doses of poliomyelitis vaccine, and the maximum recommended interval between the second and the third doses?*

A.—The maximum recommended interval between the first and the second doses of poliomyelitis vaccine is six weeks. The maximum recommended interval between the second and the third doses is twelve months.

Reconstructing Severed Fallopian Tubes

Q.—*Is it possible to anastomose and re-establish patency of the Fallopian tubes in a woman who was sterilized six years ago?*

A.—It is possible, but the chances of a plastic operation being successful depend a good deal on the method of sterilization employed and on how much, and which parts, of the tubes were removed. If, for example, the fimbriated extremities were excised it would be very difficult to restore fertility. A reconstruction operation on the middle or inner parts would involve either bilateral anastomosis of the severed tubes or reimplantation of their outer ends into the uterus. Provided too much tissue was not removed at the time of sterilization, the chances of success for these types of operations are rather higher than they are in cases of tubal obstruction caused by previous inflammatory disease. This is because the tube wall should, except at the site of the previous operation, be completely healthy.

Sex Hormones in Carcinoma of Male Breast

Q.—*What is the value of sex hormones in the treatment of carcinoma of the male breast?*

A.—Neither oestrogens nor androgens have proved very successful in the treatment of advanced cancer of the male breast. Androgens are contraindicated because they can accelerate the growth of the tumour, but oestrogens may be tried as stilboestrol 50 mg. daily by mouth. Good results, however, can be obtained by castration,[1] and stilboestrol may again be prescribed as an adjunct to this. As a last resort good remission can result from bilateral adrenalectomy or hypophysectomy.

REFERENCE

1 Treves, N., *Cancer*, 1949, **2**, 191.

NOTES AND COMMENTS

Athlete's Foot.—Dr. S. K. PANJA (Edinburgh, 3) writes: A slight addition to the answer to the question "What is a speedy treatment for chronic athlete's foot?" ("Any Questions?" June 4, p. 1751) may be of help to some readers. Athlete's foot can be treated efficiently by painting Castellani's paint twice daily and keeping the area dry. Ointments should be avoided as they may cause more interdigital maceration.

OUR EXPERT replies: I agree that Castellani's paint is a good treatment in some cases. Even with this, however, recurrences are frequent and the intense staining property of the paint is a certain disadvantage.

Zonulysis in Lens Extraction.—Dr. H. MCNEIL SYMONS (Tunbridge Wells, Kent) writes: In his reply ("Any Questions?" July 30, p. 405) the writer gives his opinion that the slightly increased risk involved does not warrant the use of this enzyme in the routine surgery of senile caratact. This opinion is not shared by many ophthalmic surgeons, and continued experience with this method which has been in use as a routine in the eye department at the Kent and Sussex Hospital, Tunbridge Wells, since April, 1958, shows that it is a reliable and safe method of intracapsular cataract extraction.

Corrections.—On p. 616 of the *Journal*, August 20, Sir John Charles should have been described as chief medical officer of the Ministry of Health and not of the United Kingdom.

In the Summary of the paper "A Survey of the Epilepsies in General Practice" (August 6, p. 416), the word methoin in the penultimate paragraph should read primidone.

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